The Journal of Allergy

VOL. 21 NOVEMBER, 1950 NO. 6

Symposium on Food Allergy

American Academy of Allergy

Sixth Annual Meeting, Los Angeles, Calif., March 6-8, 1950

CONCEPTS OF FOOD ALLERGY IMPORTANT IN SPECIFIC DIAGNOSIS

THERON G. RANDOLPH, M.D.,* CHICAGO, ILL.

ANY discussion of food allergy presupposes that the existence of inhalant allergy has been carefully appraised and controlled by means of adequate avoidance or therapy prior to and during the course of diagnostic measures designed to aid in the recognition of the etiologic roles of specific foods as allergens.

The incidence of specific food sensitivity is proportional to the relative frequency of ingestion of the various articles of the diet.[1, 2] For instance, there is little doubt that the cereal grains constitute the basis of the American diet and that the more important members of this botanical group or fractions derived therefrom are ingested more frequently than any other foods. There is also agreement among physicians who have made a particular study of the role of food allergy by means of adequate diagnostic procedures that the commonly ingested cereal grains are the most common food allergens.[2, 3] Rowe, who pioneered our clinical interest in food allergy, has emphasized for many years the importance of basic diagnostic diets eliminating the major cereal grains and, in his most recent works[3, 4] lays greatest stress on a single cereal-free elimination diet which also omits eggs and milk as well as a group of several other foods. Rinkel's experience[2, 5] as well as our own[2, 6, 7] indicates that corn and wheat sensitivity are the two most important causes of chronic food allergy, there being no statistically significant difference between the incidence of sensitivity to these two cereal grains. There is also general agreement that multiple cereal sensitivity is either very common or is likely to be readily induced in an individual already specifically sensitized to one or more members of the cereal grain botanical family.

The clinical significance of food allergy as a cause of symptoms and the relative incidence of major foods as allergens depend upon the diagnostic measures employed; this necessitates a discussion of the relative merits of various diagnostic techniques.

The statement is frequently heard that one can tell by a carefully recorded history whether or not food allergy exists as a cause of symptoms. In general,

*Instructor in Internal Medicine, Northwestern University Medical School, Chicago, Ill.

this statement is true only in respect to those articles of the diet ingested at relatively infrequent intervals, or perhaps to those foods ordinarily ingested regularly in the diet but which at least intermittently are taken only once in 3 to 5 days. Sensitivity to the first group of foods, such as pineapple, rhubarb, lobster or walnut, for instance, is rarely ever a difficult diagnostic problem. The second group, including those foods ordinarily taken once in 3 days but at least occasionally taken at less frequent intervals, might include such items as tomato, chocolate, carrot, or apple. The individual patient may or may not be aware of sensitivity to such foods. Patients are rarely ever able to detect the presence of specific sensitivity to those articles of the diet eaten regularly at least once daily, such as corn, wheat, milk, eggs, or potatoes, providing they have not been placed on some prescribed or self-induced dietary program which happened to reduce the frequency of intake of these basic foods. In such a list of the relative incidence of food allergens, patients are least likely to suspect those at the top of the listing and become slightly more proficient in the matter of detection of specific reactors as one proceeds downward from the top of such a list arranged according to the probability of sensitization.

The best explanation of the patient's failure to recognize food allergens when ingested at frequent intervals has been given by Rinkel[1] in his description of the masking effect produced by the ingestion of a food when the patient is still in a reactive phase following previous ingestions of the same food. Under these circumstances one may not expect an immediate flare of symptoms after a meal containing the allergenic food in question but instead some immediate amelioration of chronic symptoms with a subsequent and delayed accentuation of his allergic manifestations.

Certain exceptions should be mentioned in respect to the general statement that the history cannot be relied upon to indicate specific sensitivity to the commonly ingested articles of the diet. At times, the massive ingestion of a food will break through this masking phenomenon; an example is the immediate accentuation of symptoms sometimes occurring in the wheat-sensitive patient following a spaghetti dinner.

At times, a common food will cause immediately detectable symptoms when consumed in the presence of an alcoholic beverage. Of greater importance, however, is the specific effects of alcohol indicating sensitivity to the foodstuffs from which the spirits were derived. A detailed history of intolerance to specific alcoholic beverages frequently affords clues pointing toward the allergenicity of the common offending foods. For instance, the adult individual who claims that a single drink of beer or whisky will precipitate symptoms interpreted as being allergic in type is usually sensitive to corn or wheat, or both.

Other helpful information obtained from the history is the quantitative food intake,[7] indicating the number of times per day or week that the patient ingests the common food allergens. The same information may be obtained from the food diary. These data are important for, having no other reliable index in the new patient, one suspects specific sensitivity to those articles of the diet eaten most frequently; as a general rule, such a listing corresponds fairly

closely to the listing of food allergens based on probability. Exceptions in the patient's history which do not correspond to probability immediately become suspect. For instance, the individual drinking 20 cups of coffee daily is more likely to be coffee sensitive than the person taking 1 cup daily.

Rowe,[8] Rinkel,[9] Vaughan,[10] and many others interested in the diagnosis of specific food allergy by means of clinical techniques have stressed the fallibility of skin tests with food allergens as diagnostic measures. Rinkel[2] has made the most exhaustive study of this problem and the interested reader is referred to the detailed investigation of this controversial point. The term "controversial" is used in a limited sense and refers to the popular conception apparently shared by many allergists in the reliability of such procedures. In the writer's opinion, the mechanical performance and literal interpretation of skin-test techniques have done more to retard the development and acceptance of the modern concept of food allergy than any other single point. I became convinced of this position 6 years ago and since that time have abandoned the use of both cutaneous and intracutaneous skin-testing techniques in the routine diagnosis of food allergy. Skin tests seem to be of slightly greater value in the detection of specific foods as inhalants than as ingestants.

Aside from the points in the history as mentioned and the limited information of diagnostic value which may be obtained from the food diary,[2] one may approach the diagnosis of specific food sensitivity by means of one of two recommended techniques; these consist of the individual food test as developed by Rinkel[11] or the basic type of elimination diet as first used by Rowe[12, 13] and subsequently refined by him[3, 4] or by combinations of these techniques.[2] Both procedures are in keeping with what is known of the dynamic nature and mechanism of food allergy and of the probability of sensitization based on the incidence of the major foods in the diet. Both techniques are cognizant of the all-important fact that the detection of specific food allergy is dependent upon the reproduction of clinical syndromes following the reintroduction of a specific food to the dietary after a preliminary short period of complete avoidance.

The most effective and widely used diagnostic diet is Rowe's cereal, milk, egg and fruit-free elimination diet.[3, 4] In favor of such highly restricted elimination programs is the fact that a diet such as this may be applied as a routine procedure, thus saving time and effort in contrast to more individualized diagnostic clinical procedures. Rowe[14] estimates that this diet is effective in the specific diagnosis of food allergy in 75 per cent of the cases of food allergy in which he applies it. In contrast to other diagnostic diets, this diet has the further advantage of eliminating all the cereals with the exception of cane,* an important point due to the high incidence of sensitivity to rye, oats, and rice existing in the individual already sensitive to wheat or corn. It should be emphasized that corn is eliminated completely in the form of this diet currently used by Rowe.[14] The avoidance of milk, eggs, and fruit not only excludes the 4 most important food allergens but also handles the rather common problem of multiple fruit sensitivity.

*From the strict botanical sense, cane is a member of the graminae and cane sensitivity is not as rare as formerly alleged.[15]

The Ralston wheat, milk and egg-free diet is to be criticized in that it does not eliminate corn which is at least tied with wheat for first place in the incidence of specific food allergens.[2, 5, 6] Although this diagnostic diet is more applicable when used in conjunction with their restricted diet eliminating corn but the fact that rye is employed in both and the further fact that the majority of wheat-sensitive patients cannot tolerate rye materially limits the usefulness of the Ralston diets in specific diagnosis.

Although such sharply restricted elimination procedures are admirable for the individual who fortunately happens to have a relatively narrow base of sensitivity,[7] unfortunately, even the experienced clinician cannot be certain which of his patients may be so categorized prior to instituting specific diagnostic measures. The individual with a current wide base of food sensitivities is also likely to have a low inherent tolerance for foods[1] which means that he is likely to develop new sensitivities readily. Such a patient may not only fail to have a significant degree of relief of his allergic symptoms from such a restricted diet but may develop one or more new sensitivities resulting from the oft-repeated ingestion of permitted foods. All such restricted standardized dietary programs employed in diagnosis are based on the presupposition that certain selected foods are relatively low in the incidence with which specific sensitivity is diagnosed; this presupposition does not preclude the fact that all foods are potentially allergenic. The so-called less important foodstuffs immediately become potentially important food allergens when their incidence in the diet is increased; this is particularly true of the individual who develops new sensitivities readily.

The other recommended approach in the specific diagnosis of food allergy is the performance of several individual food tests with the major articles of the diet based on the individual's eating habits and the probability of sensitization. The technique of this test was developed by Rinkel[2, 11]; it consists briefly in the absolute avoidance of a particular food for 4 days prior to its experimental ingestion under observation. The incidence and severity of symptoms are recorded per unit of time by an observer trained in the technique of the test for one-half hour prior to the deliberate ingestion of the food in a fasting condition and for 3 one-half-hour periods thereafter. A second feeding is given 1 hour after the first, providing an acute symptom response has not developed. The test is considered positive if there is a doubling or tripling in the incidenc of coughing, sneezing, or other symptoms found by experience to be associated with a positive reaction.[2] Total leucocyte counts (enumerating double the number of leucocytes usually counted) are performed prior to the initial feeding and at 20, 40, and 60 minutes thereafter. In the absence of clear-cut reactive symptoms, some emphasis is given to the interpretation of the leucocyte responses, an empirical association of fairly high correlation having been shown to exist between the development of a leucopenia of 10 per cent or greater occurring in the post-prandial blood observations and in the presence of delayed or cumulative types of food reactions.[11, 16]

This diagnostic approach is advantageous in that it permits the direct observation of the patient immediately prior to and during the course of induced allergic reactions. When applied to the first 6 or 8 major allergenic foods in a patient's diet, the diagnostician learns something of the extent of involvement of the diet by the food allergy process.[2] In the event of a narrow base of sensitivity it is then safe and expeditious to proceed with highly restricted diagnostic diets. If more than fifty per cent of the first group of foods are incriminated, one then proceeds with further individual food tests without placing this type of patient on a highly restricted diet.

The chief disadvantage of this type of approach is the time and office space consumed in such tests.

Regardless of the exact methods employed, the complete avoidance of a major food for at least 4 days is an essential part of the diagnostic program, for otherwise the specifically sensitive patient may not react with clear-cut allergic symptoms when the food is reintroduced to the diet. This not only means the common forms of the foods but various fractions of the food as well. In view of the fact that this aspect of the avoidance of foods has recently been questioned,[17, 18] the allergenicity of starches, sugars, alcohols, gelatins, and oils will be briefly reviewed.

As it has long been recognized that wheat starch (flour) and potato starch will cause symptoms when ingested by specifically sensitized individuals, it is not too surprising that cornstarch should act similarly in the corn-sensitive patient. The widespread use of cornstarch and certain heretofore unrecognized sources of exposure have recently been reported.[2, 19 20]

The ingestion of corn sugar (glucose or dextrose) not only causes clinically demonstrable symptoms in the majority of corn-sensitive patients but also frequently results in more acute symptom responses than occur after the ingestion of corn as such. Both Rinkel and the author determined independently that the diagnostic accuracy of individual food tests with corn was increased if corn meal gruel and corn sugar were fed rather than testing with the gruel alone.[2, 21] In selected circumstances the intravenous injection of corn sugar has been known to be associated with the production of allergic symptoms.[22] In view of these observations it is not surprising to learn that clinical reactions may be induced by the ingestion or intravenous injection of cane sugar in certain cane-sensitive patients[15] or by the ingestion of beet sugar or monosodium glutamate prepared from Steffan's waste (beet pulp following the extraction of the sugar) in at least some beet-sensitive individuals.[23]

During the past 3 years a study to determine the specificity of alcoholic spirits in respect to the native foods from which the alcoholic beverages were derived has been in progress. Pure samples of corn, potato, and cane spirits were prepared* and tested in known sensitive patients as well as in individuals known not to be sensitive to the native food. In data as yet unpublished, it has been shown that alcoholic spirits exert a specific effect on allergic individuals in respect to the existence of sensitivity to the native food from which the spirits were derived. When comparable individual food tests were run on the same

*Prepared through the courtesy of Hiram Walker and Sons, Inc., Peoria, Ill.

individual with a large serving of the food and another time with an ounce of the specific spirits (100 proof), as a rule more acute allergic symptoms resulted from the alcohol.

Contrary to the common impression, certain patients highly sensitive to beef will have allergic symptoms following the ingestion of commercially available bovine gelatin,[24] although a similar allergenicity for the gelatin prepared for the pharmaceutical trade (Wilson) could not be demonstrated.

It is generally agreed that the oil fraction of a given food is less allergenic than other fractions. Nevertheless, there are unmistakable instances in which ingestion of the refined oil will cause allergic symptoms on certain individuals sensitive to the native food.[2, 25] Sensitivity to cottonseed oil with or without the presence of positive skin tests with cottonseed extract may also exist.[14, 26]

The general aim in the diagnosis of specific food allergy, whether by means of individual food tests with or without basic types of elimination diets, is to free the patient of current chronic allergic symptoms. In many instances this objective can be accomplished only by the elimination of the starches, sugars, alcohols, and sometimes the oils of specific foods as well as the avoidances of the food in its native or cooked state. The failure of clinicians to recognize these basic facts or the inability to instruct their patients adequately in the minutia required to accomplish the complete elimination of a food or the patient's reluctance to follow such instructions accounts for many of the apparent failures in specific allergic diagnosis. Such failures have not only reflected to the discredit of allergists but, unfortunately, commonly result in the most highly allergic individuals remaining undiagnosed. This would be bad enough, but even worse is the deduction under such circumstances that the patient is not even allergic when actually one is dealing with an advanced case of clinical allergy.

Once an individual has been freed of allergic symptoms on some type of diagnostic plan, the next stage is to return the previously omitted foods one by one and in such a timing as to note most effectively the relationship of the food to the production of symptoms. The evidence obtained may be confirmatory of points in the history or the results of earlier individual food tests. If the response upon reintroduction of a particular food to the diet is at all equivocal, it should again be omitted and subsequently returned to the diet in cumulative doses.

Once the specific diagnosis is made, then and only then should the role of the so-called "food fractions" be determined. It should be emphasized that not all corn-sensitive patients find it necessary to avoid all forms of corn and that not all milk-sensitive individuals find it necessary to avoid all traces of milk in order to have what the patient and his physician currently regard as a satisfactory degree of relief of symptoms. It is also recognized that some patients can continue on such a plan without any apparent ill effects, although it is difficult to tell in advance which individuals will take this particular course. Some patients will subsequently become intolerant to minor sources of such specific foods; an extreme illustrative case of this type has been reported by the author.[27] A more common course of events is for the patient to maintain an

active degree of sensitization to the food in question instead of gradually developing tolerance to it.

If the base of sensitivity permits, the ideal treatment of specific food allergy from the standpoint of an eventual gain of specific tolerance is the complete avoidance of the incriminated food. From a practical standpoint, this course of events is relatively easy when dealing with some foods and difficult to the point of being almost impossible with certain others. When the base of sensitivity is wide, the food-allergic individual profits by the avoidance of the most potent allergens and the use of all other foods on a rotating, diversified schedule of feedings as recommended by Rinkel.[28]

REFERENCES

1. Rinkel, H. J.: Role of Food Allergy in Internal Medicine, Ann. Allergy **2**: 115, 1944.
2. Rinkel, H. J., Randolph, T. G., and Zeller, M.: Food Allergy, Springfield, Ill., Charles C Thomas, Publisher, 1950.
3. Rowe, A. H.: Elimination Diets and the Patient's Allergies, Philadelphia, 1944, Lea & Febiger.
4. Rowe, A. H.: Nutrition in the Allergies, Wohl, Dietotherapy, Clinical Application of Modern Nutrition, Philadelphia, 1945, W. B. Saunders Company.
5. Rinkel, H. J.: Food Allergy, J. Missouri M. A. **37**: 428, 1940.
6. Randolph, T. G., and Yeager, L. B.: The Incidence of Allergy to Major Foods, J. Lab. & Clin. Med. **32**: 1547, 1947.
7. Randolph, T. G.: Food Allergy, M. Clin. North America Chicago Number, January, 1948, W. B. Saunders Company.
8. Rowe, A. H.: The Evaluation of Skin Reactions in Food Sensitive Patients, J. ALLERGY **5**: 135, 1934.
9. Rinkel, H. J.: Food Allergy, J. Kansas M. Soc. **37**: 177, 1936.
10. Vaughan, W. T.: Practice of Allergy, St. Louis, 1939, The C. V. Mosby Company.
11. Rinkel, H. J.: Food Allergy. II. Technique and Clinical Application of the Individual Food Test, Ann. Allergy **2**: 504, 1944.
12. Rowe, A. H.: Abdominal Food Allergy; Its Treatment With Elimination Diets, California & West. Med. **29**: 5, 1928.
13. Rowe, A. H.: Food Allergy; Its Manifestations, Diagnosis and Treatment, J. A. M. A. **91**: 1623, 1928.
14. Rowe, A. H.: Personal communication.
15. Randolph, T. G., and Rollins, J. P.: Allergic Reactions From the Ingestion or Intravenous Injection of Cane Sugar, J. Lab & Clin. Med. **36**: 242, 1950.
16. Randolph, T. G., and Rawling, F. F. A.: Blood Studies in Allergy, V. Variations of Total Leucocytes Following Test Feeding of Foods; An Appraisal of the Individual Food Test, Ann. Allergy **4**: 163, 1946.
17. Allergy to Refined Food Products (Editorial), J. A. M. A. **141**: 847, 1949.
18. Lee, H. J., and Squier, T. L.: Provocative Diets in the Recognition of Food Allergy, J. A. M. A. **142**: 318, 1950.
19. Randolph, T. G.: Cornstarch as an Allergen, Sources of Contact in Food Containers, J. Am. Dietet. A. **24**: 841, 1948.
20. Randolph, T. G.: Allergy to So-called "Inert Ingredients" (Excipients) of Pharmaceutical Preparations, Ann. Allergy **8**: 519, 1950.
21. Randolph, T. G., and Yeager, L. B.: Corn Sugar as an Allergen, Ann. Allergy **7**: 651, 1949.
22. Randolph, T. G., Rollins, J. P., and Walter, C. K.: Allergic Reactions Following the Intravenous Injection of Corn Sugar (Dextrose or Glucose), J. Lab. & Clin. Med. **34**: 1741, 1949 (abstract), Arch. Surg. **61**: 554, 1950.
23. Randolph, T. G., and Rollins, J. P.: Allergic Reactions From the Ingestion of Beet Sugar (Sucrose) and Monosodium Glutamate of Beet Origin, J. Lab. & Clin. Med. **36**: 407, 1950.
24. Randolph, T. G.: Gelatin as an Allergen, J. Lab. & Clin. Med. **32**: 1548, 1947.
25. Rowe, A. H.: Clinical Allergy, Its Manifestations, Diagnosis and Treatment, Philadelphia, 1937, Lea & Febiger.
26. Randolph, T. G., and Sisk, W. N.: Cottonseed Oil Sensitivity, Ann. Allergy **8**: 5, 1950.
27. Randolph, T. G.: An Unusual Case of Milk Sensitivity, J. A. M. A. **126**: 430, 1944.
28. Rinkel, H. J.: Food Allergy. IV. The Function and Clinical Application of the Rotary Diversified Diet, J. Pediat. **32**: 266, 1948.

CHANGES IN TISSUE SENSITIVITY ASSOCIATED WITH VARYING LIFE SITUATIONS AND EMOTIONS; THEIR RELEVANCE TO ALLERGY*†

DAVID T. GRAHAM, STEWART WOLF, AND HAROLD G. WOLFF, NEW YORK, N. Y.

IT IS the purpose of this paper to present further evidence on three points: (1) that man reacts adaptively or protectively in similar ways to a variety of noxious stimuli; (2) that he may react to threats or symbols of assault as though they were assaults; and (3) that consequently it may be difficult to ascertain what aspects of a total situation are really relevant to the observed reactions of the individual. In particular, ingested chemical agents and foods may sometimes take on special significance not dependent on their chemical or physical structure.

The study of cutaneous vascular reactions in patients with urticaria, reported in detail elsewhere,[1] is illustrative. Thirty subjects, 17 women and 13 men, who had had repeated attacks of hives or whose present attack had lasted for 3 weeks or longer, were studied. In each case a relatively complete life history was obtained, with particular reference to an understanding of the setting in which the first and subsequent attacks occurred. An important part of such understanding was a knowledge of the patient's feelings about the situation and his general behavior with respect to it. Note was made of foods ingested and of exposure to other substances which might conceivably have acted as allergens. It was found that there was an almost invariable relationship between an attitude of a particular kind and attacks of urticaria. The patients considered themselves wronged or injured and felt that they could do nothing to improve the situation. No correlation between exposure to allergens and attacks of the disease was discovered.

In an experimental setting, and following suitable control observations, significant events known to have been associated in the past with outbreaks of hives were brought up for discussion and dwelt on for several minutes. The experiment concluded with a period of strong reassurance and diversion. During the entire experiment measurements of cutaneous vascular reactions were carried out.

All of the patients were seen to flush when topics of significant personal concern evoking resentment were discussed. Measurement revealed that at such times there was decrease in tonus of the minute vessels (capillaries and venules) and dilatation of arterioles. In 5 cases, urticarial lesions appeared during stressful interviews. Fig. 1 illustrates a typical experiment.

Lewis[2] pointed out that dilatation of minute vessels and of arterioles, respectively, was responsible for the first two elements of the "triple response," the red reaction and the flare. The third factor, increased vascular permeability

*From The New York Hospital and the Departments of Medicine (Neurology) and Psychiatry, Cornell University Medical College, New York, N. Y.

†This paper was read by Dr. Harold G. Wolff before the Sixth Annual Meeting of the American Academy of Allergy, Los Angeles, Calif., March 6-8, 1950.

which leads to whealing, is probably simply the result of the first two.[1] He showed that the complete response was evoked by many different kinds of trauma to the skin. Erythema and whealing are, in other words, part of the response of the organism to a variety of different assaults.

The results of the experiments carried out using the patients as subjects show that exactly the same cutaneous vascular reactions may occur in response to the symbolically traumatic situations of daily life. It was, furthermore, possible to show in a healthy man that the loss of minute vessel tone which follows a blow will also take place if a blow is merely threatened (Fig. 2).

The increased readiness for vasodilatation in the skins of the patients as opposed to those of individuals without skin disease was also manifested in dermographism. Striking, moreover, was the occurrence of whealing when histamine and pilocarpine were applied by iontophoresis in concentrations lower than those which evoked responses in control subjects.

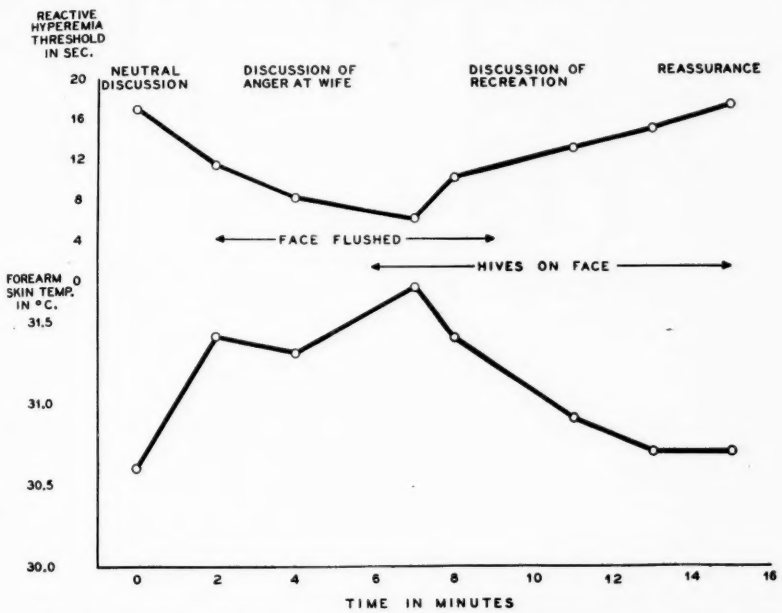

Fig. 1.—Experimental interview during which the patient developed hives. Decrease in reactive hyperemia threshold indicates loss of tone (i.e., increased tendency to dilatation) in minute vessels (venules and capillaries); rise in skin temperature indicates dilatation of arterioles. Dilatation of both sets of vessels associated with resentment culminated in the development of urticarial lesions which required some time to disappear despite reversal of the vascular changes.

In 1 patient it was possible to alter the response of the skin to histamine and pilocarpine from negative to positive, and then to reverse it again, by introduction of suitable topics for discussion (Fig. 3). In another, the same changes were demonstrated using histamine alone.

Results of study of an analogous type of allergic reaction involving the nasal mucous membrane have been presented by Holmes, Goodell, Wolf, and Wolff.[3] Nasal secretions of the subjects were collected and stained by an appropriately standardized technique before, during, and after the discussion of

significant conflicts. At the same time white blood cell counts were made on the peripheral blood. It was found that nasal hyperfunction in association with stress was accompanied by a marked eosinophilia locally and in the peripheral blood as well. The reaction is illustrated in Fig. 4. In this subject, as well as in others, not only was an eosinophilic reaction observed in company with stress, but there was also a purulent response with the outpouring by the nasal membranes of polymorphonuclear leucocytes.

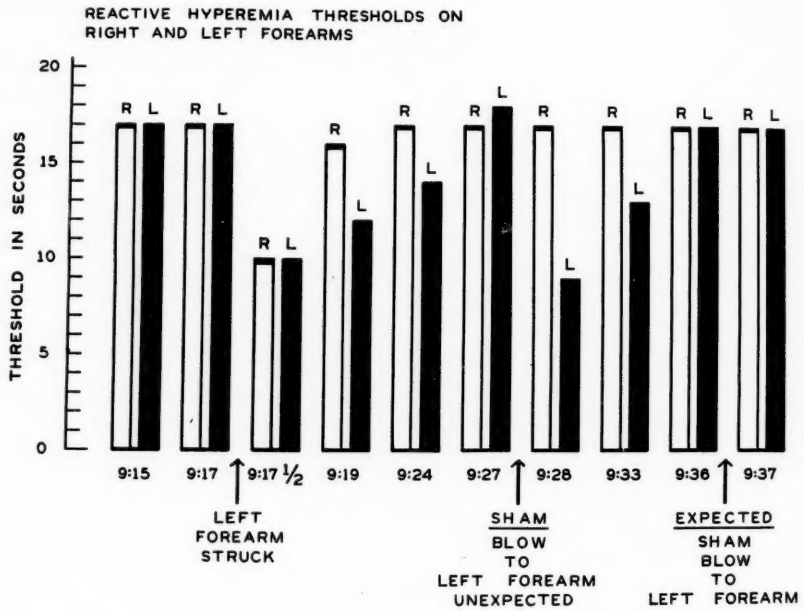

Fig. 2.—Loss of tone in minute vessels in skin of a healthy man occurring in response to a blow and to the mere threat of a blow.

Food Sensitivity

It is conceivable that foods, by virtue of particular chemical or physical structure, sometimes give rise to antigen-antibody reactions and subsequent clinical manifestations of food sensitivity. The evidence for and against the occurrence of such reactions and their importance in clinical medicine is difficult to evaluate. In any event, however, before it may be inferred that such reactions do exist and are clinically important, patients suspected of food sensitivities must be tested so as to preclude conditioning factors, since all the reactions may be exhibited in response to stimuli which have a threatening or other significance to the particular individual concerned.

It has been maintained that migraine headache is frequently a manifestation of food "allergy." The difficulties involved in reaching such a conclusion are illustrated by the following experiment.[4]

Four able physicians, experienced in experimental methods, and themselves migraine patients, were the subjects. These 4 physicians, who were of the opinion that they could predictably produce migraine headache in themselves

by eating chocolate in any form and in minimal amounts, were each given a set of lettered, sealed envelopes, with the key to the contents held in the laboratory and unknown to the subject. Each envelope contained either 8 Gm. powdered chocolate or 8 Gm. lactose in 8 black capsules. The 2 sets of capsules were indistinguishable in appearance. Two subjects ingested the contents of an envelope at convenient intervals. One subject ingested the contents at regular intervals, 3 times a week. The fourth subject, who commonly awoke on Saturday morning with a migraine headache attack after eating chocolate on Friday evening, ingested his capsules on Friday evenings for a period of 4 months. All were instructed to include no chocolate in their regular diet. Careful records were kept by each subject, including the following data: the letter on the envelope, the date and time of ingestion of the contents, the date and time of onset of all headaches experienced during the experimental period.

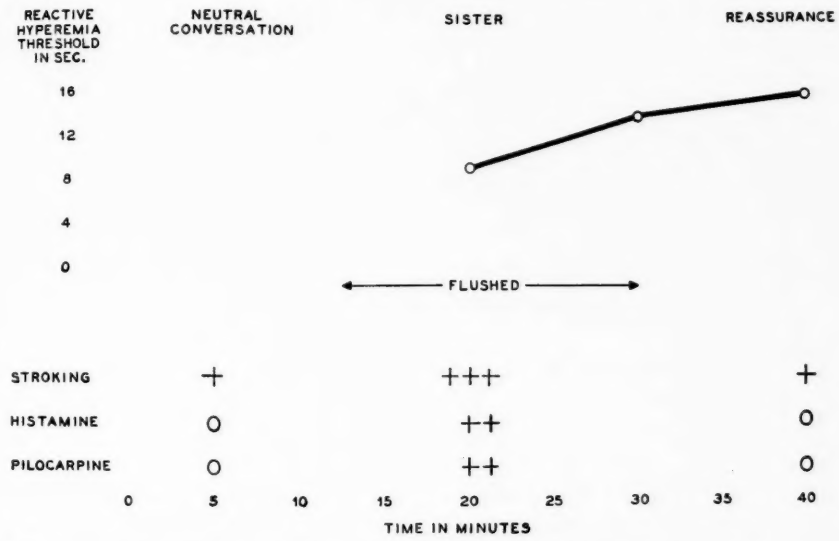

Fig. 3.—Simultaneous changes in the response of the skin to histamine, to pilocarpine, and to stroking during a stressful interview with a woman patient with hives (histamine acid phosphate 0.001 per cent and pilocarpine hydrochloride 1 per cent at 10 microamperes for 2 minutes over 1 square centimeter). There was no response to isotonic sodium chloride solution applied in the same way before, during, or after the period of stress.

It was found in these subjects that headaches sometimes followed the chocolate, sometimes the lactose, but most commonly attacks occurred without reference to the ingestion of capsules. Migraine headaches followed the ingestion of lactose just as frequently as they followed the ingestion of chocolate. The data thus accumulated indicate that, in these individuals who considered themselves "allergic" to chocolate even in minimal amounts, the occurrence of their headaches was no more related to the ingestion of chocolate than it was to the ingestion of lactose.

No well-controlled clinical study has yet been reported to support the contention that migraine headache is an allergic reaction, or to prove that the benefit from prescribed diets is specifically due to elimination of offending

allergens. It is conceivable, as mentioned above, that food sensitivity of an allergic nature does occasionally induce a headache such as has been discussed in connection with the nose. It is pointed out that the mucous membranes of the nasal and paranasal structures exhibit vasomotor changes as a part of the reaction to allergens and may give rise to headache. But in the case of the headache which accompanies the nose reaction, as well as in the case of the migraine headaches, the assumption that the allergens are responsible for the symptom must be closely questioned in any given case until proved valid.

The following observations further emphasize the necessity for caution. They were made on patients in whom food sensitivities seemed relevant to their major complaints. The patients were able to relate closely their symptoms to the ingestion of even minimal amounts of the supposedly noxious substance. A simple experiment demonstrated how unpredictable the relationship was, the reaction being apparently more dependent on seeing, tasting, smelling, and hearing of the agent than upon its chemical and physical nature.

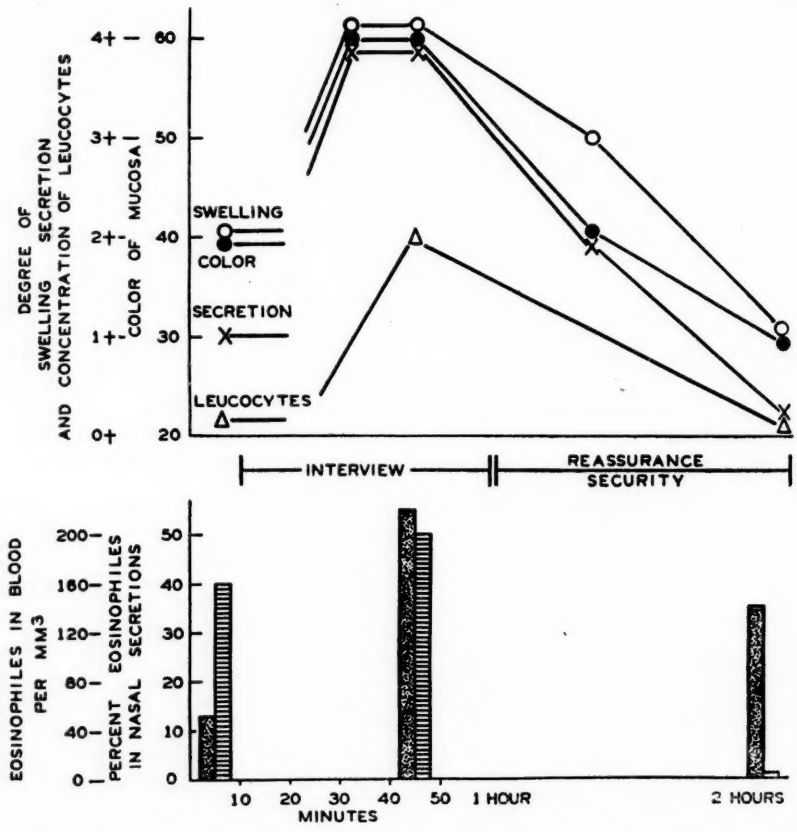

Fig. 4.—Changes in nasal mucous membrane and eosinophiles in peripheral blood during stressful interview.

CASE REPORTS

CASE 1.—A 50-year-old woman, whose chief complaints were "pressure" in her head, "poor thinking and memory," "vision not clear," "dizziness," abdominal cramps, nausea,

hives, and abdominal "bloating," was studied. The symptoms occurred within 10 to 20 minutes after ingesting milk or milk products. It was stated that 4 drops of milk in a glass of water produced attacks of the above nature. She had had these attacks for 11 years, beginning after a Caesarean section. The patient had "never liked milk" but had taken a great deal of it during this pregnancy, during which she gained 60 pounds. Soon after she was given a reducing diet, milk elicited the symptoms. Skin tests were positive to milk, tomatoes, peaches, peas, pork, and lobster, but symptoms were associated only with the ingestion of milk. The patient's last ingestions of milk had been 4 days and 8 days prior to the skin test.

On the occasion of the experiment, balloons were introduced into the stomach and duodenum. After a preliminary control period had established the approximate rate and amplitude of contractions (Fig. 5), 50 c.c. of whole milk were introduced into the fundus by stomach tube without the patient being able to observe what was being administered. She was told that she was being given water as a preliminary testing procedure. There was no significant change in the duodenal motility pattern and the patient exhibited no symptoms. About 2 weeks later the experiment was repeated. This time the patient was given 50 c.c. of tap water and she was told that milk was being introduced. As will be seen further from the diagram, she developed nausea and abdominal discomfort following this suggestion, associated with some change in the duodenal motility pattern.

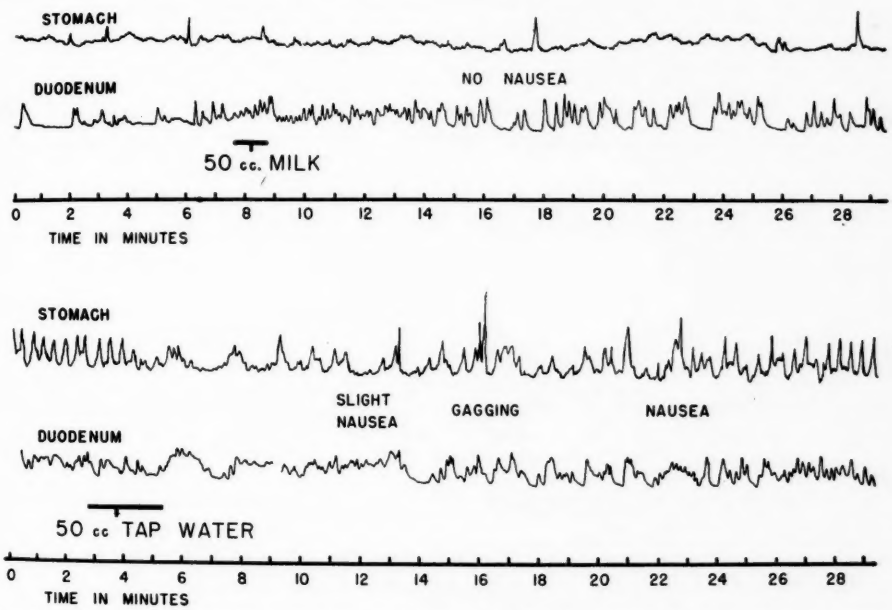

Fig. 5.—Changes in symptoms and in gastric and duodenal activity in the patient of Case 1 after the administration of milk and of tap water (see text).

CASE 2.—A 45-year-old woman, who for 28 years had had attacks of asthma within a few minutes after eating food prepared with cottonseed products, such as doughnuts, was studied. She also exhibited wheezing and dyspnea in rooms containing cotton-filled furniture. In addition she complained of abdominal cramps and nausea after eating mushrooms. Her skin and conjunctiva were sensitive to cottonseed extract. With the knowledge that she was being tested, this patient was given 1 c.c. of 100 units of cottonseed extract by mouth with no untoward results. She was then given 1 c.c. of 1,000 units of cottonseed extract by mouth which produced nausea in 9 minutes, lasting for 12 minutes. Three days later the administration of 10,000 units of cottonseed extract by mouth resulted in itchy nose and a severe asthmatic attack which persisted for 36 hours. No attempt was made to conceal from her that cottonseed was being given.

At a later date 5,000 units of cottonseed extract were given by stomach tube, the patient being told that it was water being used to test stomach motility. No symptoms ensued. Fifty minutes later, 50 c.c. of water was given and the patient was informed that she was receiving mushrooms. Nausea, abdominal pain, and bowel urgency occurred 30 minutes after the latter administration. These symptoms lasted for 20 minutes and did not recur (Fig. 6).

CASE 3.—A study was made of a 39-year-old woman who for about 3 months complained of wheezing, running eyes and nose, and hives soon after the ingestion of milk. Skin tests were positive to milk and fish. A stomach balloon was inserted and, after a control period during which motility of the stomach was observed, 50 c.c. of milk were introduced. The patient was told that the introduced liquid was water. She was then told that a specimen of gastric secretion was to be taken but actually nothing was withdrawn. Her nasal mucous membrane was examined before and after the administration of milk and it was found that there was less secretion and congestion after the milk than before. She had no wheezing (Fig. 7).

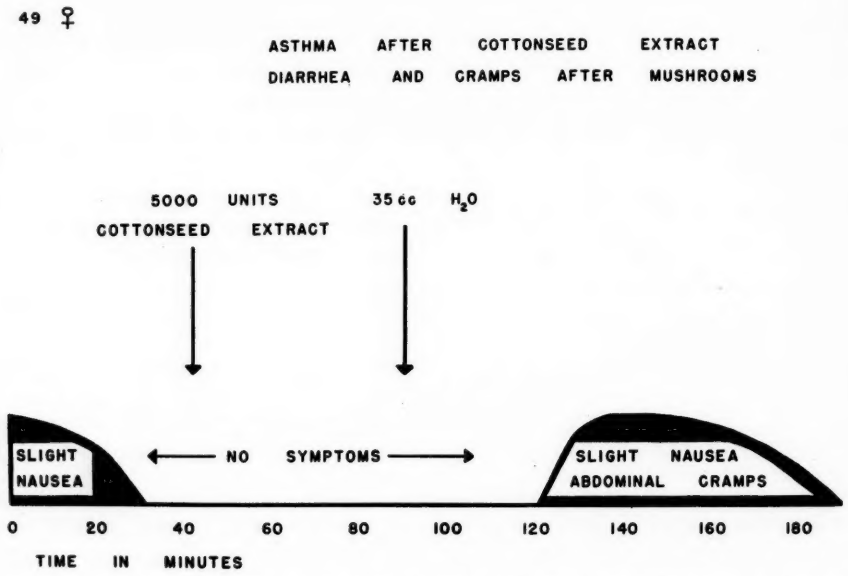

Fig. 6.—Changes in symptoms of patient of Case 2 after administration of cottonseed extract and of water (see text).

COMMENT

The inference from such demonstrations is that the relation between an ingested agent and tissue reaction may be intimate and dramatic. However, unless the circumstances of administration of the agent preclude all opportunity for conditioning factors to operate, it may not be inferred that such reactions are allergic in nature.

Thus from a series of controlled experimental studies it is inferred that arterioles and minute vessels of the skin exhibit dramatic changes in function during experimentally induced alterations in feeling states. Certain persons, during periods of resentment in reaction to symbols of assault, exhibit dilatation of arterioles and minute vessels. This constellation leads to a transudation of

fluid with resultant edema of the skin. When this is especially striking locally, it becomes tumescent edema or hives and constitutes under certain circumstances a "positive" skin test. Although such tissue alterations occur without additional mechanical stimuli from without, slight mechanical trauma, such as arises from the pressure of clothing or gentle blows, augments locally the edema in the skin. A great variety of nonspecific agents may become factors in the outward show of dermatoses when the skin is already in such a state of increased sensitivity. Moreover, the skin changes in its sensitivity to chemical agents so that amounts of histamine which under one set of life circumstances and emotions produce no reaction may, under others, evoke urticarial reactions. Indeed, during periods of stress, skin and mucous membranes may exhibit an increased sensitivity to a host of foods, pollens, drugs, and simpler chemical agents. Such increased sensitivity is not present during periods of relative tranquillity.

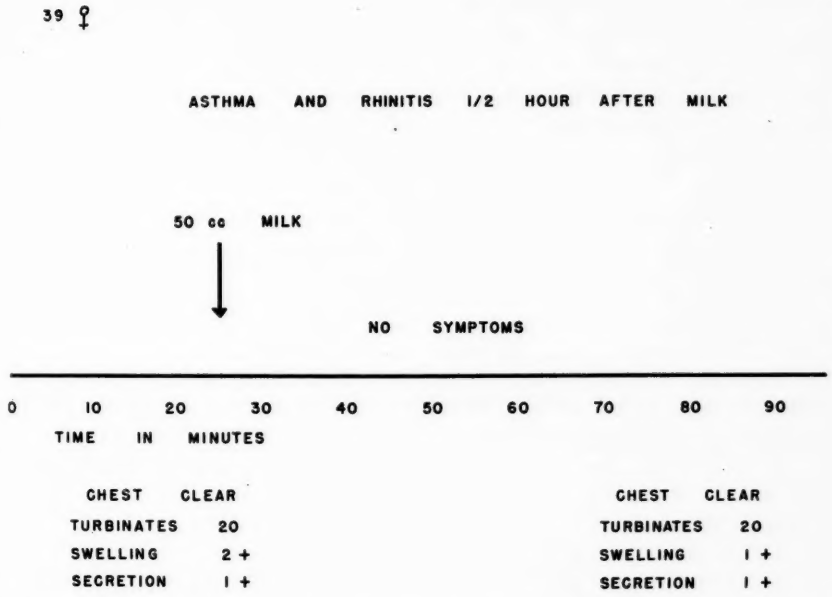

Fig. 7.—Slight decrease in edema of nasal mucosa, without change in secretion or in color of turbinates, after administration of milk. No symptoms developed. (See text, Case 3.)

It has also been shown that foods ingested under one set of conditions are followed by violent reactions which are absent when the same substances are ingested under other conditions. Therefore, in assaying the tissue sensitivity of an individual to certain assaults, including ingestion of foods, it becomes necessary to appraise their effects in terms of the setting and feeling states under which they are administered. Without such appraisal the nature of the sensitivity reaction cannot be accurately defined. It is obvious that summation of the effects of various factors is often important, and for optimal therapeutic effectiveness those which are most important must be defined and dealt with.

CONCLUSIONS

The same adaptive or protective reactions may occur in man in response to many different stimuli. The physician aims to define that aspect of the situation which is most pertinent to the given individual and proceed accordingly.

REFERENCES

1. Graham, D. T., and Wolf, S.: The Pathogenesis of Urticaria, J. A. M. A. **143**: 1396, 1950.
2. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, 1927, Shaw & Sons, Ltd.
3. Holmes, T. H., Goodell, H., Wolf, S., and Wolff, H. G.: The Nose, Springfield, Ill., 1950, Charles C Thomas, Publisher.
4. Wolff, H. G.: Headache and Other Head Pain, New York, 1948, Oxford University Press.

SYMPOSIUM ON FOOD ALLERGY: THE INTERNIST'S VIEWPOINT*

WALTER L. WINKENWERDER, M.D., BALTIMORE, MD.

IN THE opinion of this speaker, the present diagnosis of food hypersensitivity rests almost exclusively on clinical observation. Skin tests to foods even when found positive in such allergic states as atopic eczema, asthma, rhinitis, and urticaria rarely indicate specific clinical sensitivity. The possibility of discovering specific food sensitivity by doing skin tests either by the scratch or intradermal method in any allergic state is definitely remote and I have routinely omitted such tests for several years; even in patients in which by history food hypersensitivity appears to be likely, supporting evidence in the form of positive skin reactions to the specific food involved is rarely found. Furthermore, it is true that not only skin reactions and also serum reagins to many foods are demonstrable in many patients, particularly in the pollen-sensitive group, but the corresponding foods rarely are of clinical significance since ingestion of such foods usually fails to elicit specific symptoms. This striking lack of correlation between skin reactions to food antigens and clinical experience have been and is becoming more widely recognized to the extent that not a few allergists have practically abolished skin testing to foods as a routine procedure.

As an internist interpreting experience in allergic states I am, therefore, most skeptical of a diagnosis of food hypersensitivity when such a diagnosis is based primarily on skin tests, and furthermore this skepticism is the greater when some vague clinical syndrome, such as fatigue states, headaches, various gastrointestinal complaints, including chronic indigestion and mucous colitis, are attributed to food allergy. The diagnosis of specific food hypersensitivity versus food idiosyncrasy may be difficult and even impossible. The mere fact that elimination of a food or foods abolishes a certain symptom complex and reingestion of foods elicits the same symptoms again does not necessarily prove allergic hypersensitivity. The mechanism of the production of these symptoms by certain foods, positive skin tests notwithstanding, may be due to some as yet undiscovered physiologic disturbance not related to an allergic mechanism.

The demonstration of food hypersensitivity in the presence of chronic emotional tension states manifested especially by gastrointestinal symptoms or headaches frequently confronts the internist. As has been described in this symposium, the emotional state of the patient may modify the skin reactivity to antigens and this fact must definitely be taken into consideration in the differential diagnosis. In such patients the presence of positive skin reactions to various foods reported by the allergy consultant may well confuse the judg-

*Presented at the Sixth Annual Meeting of the American Academy of Allergy, Los Angeles, Calif., March 6-8, 1950.

ment of the internist, and as an internist a diagnosis of food allergy in such individuals is only accepted when repeated clinical trial indicates that such actually exists. Whether an allergic mechanism underlies the production of symptoms in such individuals when symptoms are produced on repeated ingestion is difficult of proof, and as stated above the particular symptoms under consideration may not be based on a definitive allergic mechanism.

At the present time more decisive diagnostic methods to prove the presence or absence of food allergy than presently available are necessary to quickly and adequately come to a conclusion. The "blind" ingestion studies just presented by Dr. Loveless* and others appear to offer one method which can be applied clinically under controlled conditions.

*See articles on pp. 489 and 500 in this issue.

MILK ALLERGY: A SURVEY OF ITS INCIDENCE; EXPERIMENTS WITH A MASKED INGESTION TEST*†

MARY HEWITT LOVELESS, NEW YORK. N. Y.

WHEREAS most authorities list milk among the three leading foods to act as excitants, there is a marked difference in opinion as to the frequency and importance of ingestant hypersensitiveness in general. If the views of Rowe, Rinkel and Randolph[1,2,3] are correct, most cases are overlooked. They place particular emphasis on chronic or "masked, smoldering" responses arising from the oft-repeated ingestion of corn, wheat, milk, and other frequently ingested foodstuffs.[4] They include among its symptoms not only the classical and borderline expressions of atopy but such atypical states as fatigue, drowsiness, chilliness, and aching or drawing sensations in the muscles.

Everyone agrees that the results of cutaneous tests may be highly misleading in food allergy. For this reason, other diagnostic approaches have been tried, such as food diaries, elimination diets, provocative diets,[5,6,7] and ingestion tests with or without associated studies of blood cytology.[8] Many physicians still feel that nothing replaces a carefully taken history. So controversial is the whole subject that the author thought it worth while to explore two of its phases: first, its incidence, by means of a poll of physicians most likely to encounter it; and second, its diagnosis, as gauged by a specially designed ingestion procedure which called for masking of the suspected food and for placebo feedings. It was expected that these precautions would minimize the influence of psychologic, physiologic, and other extraneous factors on the diagnosis. The investigation was focused on corn and milk, the present report covering the latter.

MATERIALS AND METHODS

Questionnaire.—Inquiry was made concerning: (1) the specialty of the physician, (2) the approximate number of new patients acquired during the past 5 years, (3) the number of these patients considered allergic to milk by clinical standards, and (4) the number reactive by cutaneous test.

Intracutaneous Tests.—By using several dilutions of allergen in volumes of 0.02 c.c., it was usually possible to determine the approximate dose which was required to provoke a maximal wheal-and-flare reaction in the 20 members of our experimental group. The solutions were standardized according to their content of precipitable nitrogen (phosphotungstic acid being the precipitant), 0.1 mg. representing 10,000 "protein" nitrogen units. Most of the 20 individuals examined by this test were also studied with lactalbumin, which was routinely prepared by our laboratory, and with casein and highly purified crystalline β-lactoglobulin supplied kindly by Thomas L. McMeekin,[9] Head, Protein Division, Eastern Regional Research Laboratory of the U. S. Department of Agriculture,

*From The New York Hospital and the Department of Medicine of Cornell University Medical College, New York, N. Y.

†Presented in part at the Sixth Annual Meeting of the American Academy of Allergy in Los Angeles, Calif., March 6-8, 1950.

Philadelphia, Pa. An occasional patient was also studied with his α-casein and β-casein fractions. It was hoped that the derivatives might prove more reliable diagnostic aids than had whole milk.

Ingestion Procedure.—Fresh, certified but unpasteurized milk, freed of its cream, was administered in a volume adjusted to the anticipated susceptibility of each patient. Every attempt was made to prevent the subject from learning on which occasion milk was involved. The placebo consisted of one of three commercial antacids, Amphojel, Basaljel, or Titralac (see footnotes, Table II), mixed with water on one occasion and with milk on another. The consumer was asked to close his eyes and his notrils until after the meal had been brought into the room and swallowed. An independent technician decided which feeding was to include milk and prepared both meals in an adjacent room without informing the patient or the physician of their identity. Cutaneous tests with milk were not done on days of placebo testing.

The tests were conducted according to the prerequisites of Randolph in several particulars, viz., milk was rigorously excluded from the diet for at least 4 days preceding each test and was advocated as part of the daily intake for at least 4 days prior to this exclusion period. The patient sat quietly in the fasting state for one-half hour after reaching the office; all suggestive manifestations were recorded in detail, not only for the ingestive period but for the 48 hours preceding and following it. The patient avoided or recorded the use of drugs as well as of any exposure to other allergens which might complicate the postingestive period. Occasionally, when it was impossible to arrange a second visit, the placebo feeding was presented first and later in the morning the masked milk was offered.

Finally, comparisons were set up between the diagnosis as arrived at through ingestion studies, history taking, intracutaneous test, and a reinterpretation of the ingestion result by the criteria of Randolph and others.

FINDINGS

Incidence of Hypersensitivity.—Table I indicates that 142 physicians belonging to the American Academy of Pediatrics or the American Academy of Allergy responded to the questionnaire by estimating that 4,260 of their patients showed cutaneous allergy toward milk. Since they were attending nearly 180,000 individuals, this meant an incidence of 2.3 per cent. When the figures for this population were added to those of another 49 pediatricians who do not perform cutaneous tests to diagnose food allergy, it was learned that the incidence of milk hypersensitiveness according to clinical standards amounted to only 1.5 per cent. Nearly 250,000 patients were under consideration. The questionnaires had been sent almost exclusively to physicians in the vicinity of Greater New York City with the idea that suitable material for ingestion tests might be uncovered. Figures are not included for Randolph, Rinkel, Rowe, or their followers. The result would have been considerably altered had this been the case, for these men arrive at incidences 5 to 10 times higher by the use of food diary, ingestion, and elimination procedures in combination with atypical symptoms.

TABLE I. INCIDENCE OF ALLERGY FOR MILK

NUMBER OF PHYSICIANS	NUMBER OF PATIENTS IN SURVEY	NUMBER ALLERGIC	INCIDENCE (%)
	As Judged by Cutaneous Test		
142*	179,434	4,260	2.3
	As Judged by Clinical Standards		
191†	244,719	3,691	1.5

*Internist allergists, 32; pediatric allergists, 8; pediatricians, 29; allergists, 69; dermatologists, 3; otolaryngologist, 1.

†Above group plus 49 pediatricians who did not do skin tests.

Ingestion Studies.—Table II presents in some detail the salient points of the history and the results of feeding and intracutaneous tests for 8 subjects in our experimental group. The data for these 6 adults and 2 boys have been arranged according to their histories for allergy toward milk. Each individual will now be briefly discussed.

CASE 1.—There could be no doubt as to the susceptibility of the woman, WEI, for her diagnosis was unequivocal by any standard. She gave a story of repeated asthmatic responses promptly after the ingestion of the smallest traces of milk. A sore mouth and urticaria were also very prone to occur some hours later. When a scratch test was done with whole milk a few days before she was referred to us, the wheezing was so severe that 2 injections of epinephrine had to be administered.

Our ingestion result was equally convincing. After having been entirely well for 12 days, she took water mixed with Basaljel with no reaction except slight belching and nausea which we attributed to the character of the placebo. She was symptom-free in 15 minutes and remained so for another one-half hour, at which time 1½ oz. of milk were served mixed with flavored Basaljel. Eructation occurred as before but was now associated with wheezing. After one-half hour, another 3 oz. of milk were taken. Asthma of moderate severity ensued within 15 minutes. By the time her observation period was over it had subsided somewhat, but it persisted in mild form through the rest of the day.

Five days later, the experiment was repeated with peppermint-flavored Amphojel as the placebo as a substitute for Basaljel. It was mixed with 90 c.c. of tap water. No symptoms developed during the one-half hour following this placebo feeding. One and one-half ounces of milk containing the flavored placebo material were then offered, with the production of definite asthma in 15 minutes. The attack remained at its moderately severe level after another feeding of 3 oz. in 30 minutes and a third meal of 9 oz. in 60 minutes. The final specimen elicited nausea and vomiting as well as a pruritic erythema of neck and chest. We later learned that she developed generalized urticaria that evening.

CASE 2.—The young man, GIA, in Group 1, stated that one-half a tumblerful of milk would cause nausea and abdominal cramps after 4 hours, and that 1 or 2 glasses led to diarrhea. His history was complicated by the impression that various vegetable gums, pork, lamb, citrus fruits, raw vegetables, and fatty foods often provoked similar upsets. Extracts containing as few as 10 protein units of milk or its fractions gave rise to significant cutaneous responses, placing him in the +++ class. Whereas our placebo ingestion test with 2 tablets of Titralac in 8 ounces of water was well tolerated, a similar volume of milk with Titralac taken on another morning caused mild indigestion and distention after 2 hours.

It was taken for granted that both these cases would have yielded results comparable to those described for our ingestion experiments had the subjects been aware that milk was involved. They have, therefore, been rated as positive for milk allergy according to the Randolph criteria as well as by the other diagnostic approaches. The correlation between the several methods can be readily seen in Table III. It refers to the 8 members of the ingestion covered by Table II.

TABLE II

PATIENT	HISTORY OF RESPONSE TO MILK INGESTION	RESULTS OF INGESTION EXPERIMENTS WITH MILK		RESULTS OF INGESTION TESTS WITH PLACEBO		RESPONSE TO INTRACUTANEOUS TEST WITH 0.02 C.C. OF EXTRACT (STRENGTH IN PTA-NITROGEN UNITS PER C.C.)			
		VOLUME IN MEAL	CLINICAL RESULT	PLACEBO	CLINICAL RESULT	SKIMMED MILK	LACT-ALBUMIN	BETA-LACTO-GLOBULIN	CASEIN
Group I: History Definitely Indicative of Milk Allergy									
1. WEI	Asthma +++ in 10 min. Stomatitis, hives 12 hr. after even traces of milk	135 c.c. + Basaljel* 375 c.c. + Amphojel†	Nausea ++ in ¼ hr. Asthma ++ in ¼ hr. for 8 hrs. Nausea, vomiting ++ in ¼ hr. Erythema neck, chest in ¼ hr. Asthma ++ in ¼ hr. Hives in 12 hrs. +++	90 c.c. water with Basaljel	Nausea ++ for ¼ hr. in ¼ hr.	(Scratch test= slight + with systemic in 10 min.)			
2. GIA	Nausea, vomiting, colic 4 hrs. after milk, 8 oz., or lamb, pork, vegetable gums, citrous fruits, raw vegetables, fats	240 c.c. + Titralac‡	Mild indigestion and abdominal distention in 2 hrs. for 24 hrs.	240 c.c. water + 2 tablets Titralac	Negative	5 u/c.c.=++ 10u/c.c. = +++ salt = +±	10 = +++±	10 = ++±	10 = ++±
3. HI	Nausea, abdominal colic, 10 min. after milk; fluid retention, marked edema poor vision, memory, and thinking in several hours. Occasional hives	50 c.c. by stomach tube (with suggestion water only was being given)	Negative	Water by stomach tube with suggestion of milk	Positive	1000 = + 100,000 = ++	10,000 = ±	10,000 = 0	20,000 = ±

4. BA	One glass of milk causes abdominal cramps and coughing in 10 min.	200 c.c. + Basaljel	Momentary near-syncope in 20 min.	90 c.c. water + Basaljel	Chilly for 1½ hr. Drowsy in 45 min.	10,000 = +++	10,000 = 0	10,000 = 0	20,000 = 0
Group II: Presumptive History for Milk Allergy									
1. BLU aet 15	Asthma + after glass milk. Tolerates 2 tsp. milk, ice cream, butter, cheese. Grass, ragweed, danders also allergenic	600 c.c. during 1½ hr. + Basaljel	Asthma + in 12 hrs. for 3 hrs.	200 c.c. water + Basaljel (preceding milk test on same morning)	Negative for ½ hr. observed before milk given	10,000 = ++ salt = 0 100,000 = ++	10,000 = 0	10,000 = ±	20,000 = ±
2. RU	Tolerates 1 glass per week but 3 per week causes itchy rash dorsum both feet	250 c.c. + Basaljel	Headache +++, nausea +, drowsy + in 45 min. Itchy rash dorsum one foot in 7 days	150 c.c. water + Basaljel	Pre-existing headache + became ++ in 45 min. after ingestion	1000 = + 10,000 = +++	10,000 = 0	10,000 = 0	20,000 = 0
Group III: History Negative for Milk Allergy									
1. HA	Sense of fullness if drinks quart milk; otherwise tolerates it well	250 c.c. + Basaljel	"Restless, dizzy" for 36 hrs. but ate only 1 sandwich, orange juice, broth.	Not tested		10,000 = + 100,000 = ++± salt = 0	10,000 = 0	10,000 = 0	20,000 = 0
2. ZI aet 10	Infantile eczema + asthma from milk + other foods. Tolerates unlimited evaporated milk	250 c.c. + Basaljel	Negative	Not tested		1000 = ++± salt = 0	1000 = ++	1000 = +	1000 = +

*Basaljel (Wyeth, Inc.), an aluminum carbonate gel, flavored with vanilla (synthetic).

†Amphojel (Wyeth, Inc.), an aluminum hydroxide gel for hyperacidity; a mild local astringent free of alkalis; represents 4 per cent of aluminum oxide, peppermint flavored.

‡Titralac (Schenley Laboratories); one tablet contains 0.15 Gm. glycine and 0.35 Gm. calcium carbonate. Titration curve similar to that of fresh milk.

CASE 3.—HI was a housewife who gave a history of prompt nausea, cramps, and diarrhea after drinking milk. She also felt that she retained fluids, became slightly edematous all over, gained pounds of weight and had pressure in her head as well as vertigo, faulty memory, and impaired vision some hours after ingesting this food. That these manifestations were related to the "suggestion" of milk rather than to its allergens was shown by Dr. Harold Wolff and his associates who describe their experiments in another article of this issue. Their feedings were administered through a stomach tube, with "reversed" suggestions for the placebo and the milk. Diagnostic methods which fail to appraise the psychologic factor would have failed miserably in this case. The history and the cutaneous indications were equally misleading, as shown in Table III.

TABLE III. MILK ALLERGY AS DIAGNOSED BY HISTORY IN COMPARISON WITH MASKED INGESTION TEST, RANDOLPH CRITERIA, AND INTRACUTANEOUS TEST

PATIENT	HISTORY	MASKED INGESTION	RANDOLPH CRITERIA	INTRACUTANEOUS TESTS	
				WHOLE MILK	FRACTIONS
Group 1: History Positive					
WEI	+ (definite)	+ (definite)	+	++	
GIA	+ (probable)	+ (slight)	+	+++	++±
HI	+ (definite)	0	+	+	0
BA	+ (definite)	0	+	++	0
Group 2: History Suggestive					
BLU	+ (probable)	+ (possible)	+	+	0
RU	+ (probable)	+ (possible)	+	++	0
Group 3: History Negative					
HA	0 (definite)	0 (probably)	+	+	0
ZI	0 (probably)	0 (definitely)	0	++±	+
Consistent with history		6	7	6	2
Inconsistent with history		2	1	2	5

It seems likely that the fourth member of Group 1, BA, was also neurotic, for her story that acute abdominal pains and coughing would promptly result from the ingestion of a glass of milk did not materialize when she was given 200 c.c. of milk mixed with Basaljel, without being aware of the milk content. Aside from a momentary spell of weakness, bordering on syncope, there were no developments. During her control experiment 6 days earlier, BA had complained of persistent cold feet in spite of a warm room, and of drowsiness 45 minutes after the feeding. Although Randolph and others would interpret these symptoms as allergic, the patient had taken nothing but Basaljel in water, and the same placebo was later used in her milk feeding without eliciting either of these complaints. If our conclusion is correct, that this patient was not susceptible to ingested milk, then her intracutaneous response was misleading in the case of whole milk but reliable with the fractions, as Table III indicates.

Thus, whereas all 4 members of Group 1 gave positive histories for milk allergy, only 2 of them could be confirmed by ingestion test. They would all have been deemed positive by Randolph and Rinkel, due to the lack of control feedings and the wide latitude of acceptable symptoms. Intracutaneous findings were misleading for 2 cases in the instance of whole milk, whereas the fractions appeared to be reliable in the 3 individuals tested.

Similar investigations pursued with Group 2 were less instructive because their histories as well as their ingestion results were difficult to interpret.

CASE 1.—The 15-year-old boy, BLU, explained that he tolerated 2 tsp. of milk used in his coffee, also ice cream and cream cheese, but that a glass of milk precipitated an attack of asthma in 6 or 7 hours. The placebo feeding of water and Basaljel evoked no symptoms.

Since he was not enthusiastic about returning, he was given during the same morning a total of 600 c.c. of masked milk in 3 one-half-hour servings. There were no consequences until 12 hours later when a mild, 3-hour attack of asthma developed. In spite of his complicated history of pollen asthma, nonseasonal nasal allergy, and positive cutaneous responses to several varieties of animal dander, we listed his ingestion result as "possibly" positive. The Randolph criteria led to the same conclusion. Cutaneous reactions were observed for whole milk but not to its derivatives.

CASE 2.—The other member of Group 2 was Ru, a woman who was certain she could take 1 glass of milk without consequences but that 3 glasses during a week's time would lead by the eighth day to an itchy eruption on the dorsum of each foot. On the morning of her placebo feeding of water and Basaljel, a pre-existing mild headache was made somewhat worse. On another morning the drinking of 250 c.c. of milk mixed with the same placebo was productive of mild nausea, drowsiness, and marked cephalalgia after 45 minutes. When seen 7 days later she had a freshly erupted patch of atopic dermatitis on one foot. We somewhat hesitatingly attributed this to the milk ingestion test, in spite of the long "incubation period." According to the Randolph standards the results of both the milk and the control meal were indicative of allergy. It was unfortunate that additional studies could not be arranged to appraise the possible roles of the placebo, extraneous allergens, and psychologic factors. Table III shows that her cutaneous reactivity toward whole milk was ++ whereas there was no observable susceptibility to its fractions.

The data were more valid, particularly with reference to history and ingestion study, in the cases of the 2 members of Group 3 (Tables II and III).

CASE 1.—The adult male, HA, had been concerned over his positive cutaneous response to milk, although he had never experienced any difficulty from milk, except when he consumed an entire quart and felt temporarily distended! It came as somewhat of a surprise, therefore, when he telephoned, 2 days after our milk ingestion test with 8 oz., that he had been dizzy and restless for the ensuing 36 hours. On further inquiry, it was discovered that his eagerness to comply with our instructions to avoid all possible complications was so great that he ate nothing more than 1 sandwich, some orange juice, and broth during that period. It seemed logical to attribute his complaints to deficiency in nourishment. Hence, although the result is listed as positive by Randolph criteria, it was considered negative by our own. Slight responses were obtained with whole milk but none to fractions during intracutaneous tests. It is our hope to be able to do additional ingestion studies on this man.

CASE 2.—With the boy, ZI, the ingestion of 250 c.c. of milk was without effect. Although he had been permitted unlimited amounts of evaporated milk, his parents had withheld ordinary milk because it had provoked both asthma and eczema during his infancy. In spite of this negative ingestion response, as judged by both our own and the Randolph standards, the boy reacted almost markedly to intracutaneous injections of both whole and fractionated milk.

Summarizing these comparisons among the several diagnostic methods, it will be seen at the foot of Table III that our ingestion results were in agreement with the history in 6 of the 8 trials. The Randolph interpretation yielded 7 conclusions in keeping with the history. The intracutaneous test paralleled the history in 6 cases when whole milk was involved, but in only 2 of the 7 individuals tested with derivatives.

More crucial comparisons could be made, however, if the ingestion results were taken as the true index to the diagnosis. Table IV is a rearrangement of the same data on this basis. It will be seen that one-half the 8 cases were positive by ingestion, the remainder negative. Our results were confirmed by the Randolph standards in 5 instances, by the history in 6, and by cutaneous

studies with whole milk in 4. Thus, the history stood next to the ingestion result in reliability whereas the skin test was last. Although the fractions afforded essentially the same proportion of correct answers as did whole milk (4 out of 7), this was dependent on their tendency to give negative responses. Whole milk, on the contrary, proved active in all members of the group. That this difference was not due to degradation of the fractions during their preparation was indicated by the positive responses of Gia to concentrations as low as 10 protein units per c.c. Even higher dilutions of these derivative allergens gave unequivocal reactions in an infant to be discussed below.

TABLE IV. MILK ALLERGY AS DIAGNOSED BY INGESTION TEST IN COMPARISON WITH DIAGNOSIS BY HISTORY, INTRACUTANEOUS TEST, AND RANDOLPH CRITERIA

PATIENT	INGESTION TEST	HISTORY	INTRACUTANEOUS TEST		RANDOLPH CRITERIA
			WHOLE MILK	FRACTIONS	
WEI	Definite positive (2 tests)	Definite positive	++		Positive
GIA	Positive for slight allergy	Definite positive	+++	+++	Positive
BLU	Probably positive	Probably positive	+	0	Positive
RU	Possibly positive	Probably positive	++	0	Positive
BA	Negative (psychologic)	Definite positive	++	0	Positive
HI	Negative (psychologic)	Definite positive	+	0	Positive
HA	Negative (physiologic)	Negative	+	0	Positive
ZI	Negative	Probably negative	++±	++	Negative
Tests consistent with ingestion results		6	4	4	5
Inconsistent with ingestion results		2	4	3	3

Intracutaneous Studies in 12 Other Subjects.—A brief report will be made on 12 individuals who were investigated by history and cutaneous tests but not by ingestion procedures, largely because a goodly proportion of them were infants who might have been thrown into acute exacerbations of asthma or eczema by this test in its present crude form. There were 6 cases of atopic eczema or dermatitis in the group, 4 of acute gastrointestinal disturbance (1 also had bronchial asthma), and 2 who were not allergic to milk. Using the history as the second-best index to sensitiveness, we assorted them into 4 classes as shown in Table V. Each was then subdivided according to the reactivity noted during intracutaneous tests with whole milk. With the 3 exceptions designated, the figures given in Table V also apply to the fractions of milk. No clear-cut pattern could be found for either type of allergen, there being negative cutaneous findings in patients positive by history and vice versa.

A few lines should be devoted at this point to the unusual case of Un, a Negro boy, aged 1 year, whose marked asthma and eczema had been provoked and controlled repeatedly by the giving or witholding of milk. Intracutaneous test with milk derivatives in concentrations of only 0.01 protein nitrogen unit per c.c. elicited the following responses: lactalbumin, ++++; β-lactoglobulin,

+++; casein, +± alpha and beta caseins were negative in this strength, the latter also failing to provoke any significant reaction in concentrations of 0.1 and 1.0 units. Prausnitz-Kustner tests were positive with 10 unit solutions of lactalbumin and of β-lactoglobulin, but were only questionably so for whole casein. β-casein was active in 10 unit strength and must have accounted for the response finally provoked by whole casein when employed in 1000 unit concentration, for α-casein proved inactive even with 10,000 unit solution. Enough of this infant's serum was on hand to permit one cross test to be done. A serum site no longer reactive to β-lactoglobulin developed a maximum wheal and flare when tested with whole casein, thus indicating that the specificity of the latter differed from that of the globulin fraction.

TABLE V. CORRELATION BETWEEN CLINICAL HISTORY AND INTRACUTANEOUS TESTS FOR MILK ALLERGY

HISTORY FOR MILK ALLERGY	NO. OF CASES	INTRACUTANEOUS SENSITIVITY CLASS*			
		+++	++	+	NEGATIVE
Definite	4	1		1	2
Suggestive	2			2†	
Questionable	4			1‡	3
Negative	2		1	1§	

*For whole milk; also for fractions except where otherwise noted.
†Toward fractions, one patient was +, one patient 0.
‡Casein reaction ++, lactalbumin 0, β-lactoglobulin +.
§No tests done with fractions.

Because casein enjoys the reputation of causing allergy very infrequently, it should be remarked that there were 3 definitely positive reactors among our series of 12 patients; and it can be seen in Table II that there were 2 others among the 7 tested with it in the ingestion group. Unfortunately, no feeding experiments with any milk fractions could be carried out due to the scarcity of the highly purified material.

Diagnostic Significance of Intracutaneous Responses to Whole and to Fractionated Milk.—A few simple comparisons were set up to determine whether fractions might be superior to whole milk in intracutaneous tests. For this purpose 9 cases were selected in which the diagnosis was unequivocal for the presence or the absence of milk allergy as judged by ingestion test and/or history. (Three were positive by ingestion test, 3 by history only; the remainder were negative by one or both criteria.) Cutaneous test provided false negative results in 1 instance with whole milk, in 3 with fractions. The false positive reactions were 3 with whole milk and 2 with its derivatives. Thus each type of allergen gave misleading information in about one-half the trials, milk erring in the direction of false positives, and the fractions tending to provide false negatives. Obviously the trials were too limited to carry statistical weight.

SUMMARY AND DISCUSSION

Judged by a poll of 191 physicians, the incidence of allergy to milk is low, amounting to only 1.5 per cent when diagnosed by clinical standards and to 2.3 per cent by cutaneous tests. The questionnaires were sent to pediatricians and allergists, specialists whose encounter with this disorder should be maximal. By inference, the occurrence of this malady must be rare among the general

population. Such a statement stands in striking contrast to the opinions of Randolph, Rinkel, and Rowe who regard milk and food allergens as highly important excitants. One reason for this is that they include signs and symptoms which generally are not accepted as allergic by most physicians. Among these are fatigue, drowsiness, headache, chilly sensations, and pains or "drawing" of the muscles. The writer certainly gained the impression that allergy for milk is unusual when trying to locate subjects suitable for ingestion studies during the past 1½ years, only 20 being procured. It should be stated, however, that no effort to determine the true incidence of milk hypersensitiveness will be rewarding until more scientific means of diagnosis have been found than those in current use.

The present investigation was an exploratory excursion into a primitive area of allergy, combined with an attempt to devise a more satisfactory approach. Eight patients, selected on the basis of their histories for the existence or absence of allergy toward milk, were given milk in masked form in conjunction with control, or placebo, feedings. The conditions surrounding the test were those prescribed by Rinkel and Randolph. As in the case of 12 other subjects, they were also studied by intracutaneous tests with whole milk and its individual proteins. Comparisons were then drawn among the various diagnostic methods. When the ingestion result or a clear-cut history was used as the yardstick, the intracutaneous method appeared to produce a number of false positive responses. Its fractions, on the other hand, tended to err in the opposite direction.

Reinterpretation of our ingestion results according to the Randolph criteria brought positive findings for 3 individuals whose manifestations were judged by us to be psychogenic or physiologic rather than allergic. The placebo feedings given 2 of these subjects had clarified the diagnosis. In spite of our effort to screen out such subjects through history taking, 1 of our 8 ingestion cases was clearly, and another was presumably, neurotic—"allergic" to the idea but not to the allergens of milk! This situation is not surprising in view of the association of milk with reproductive functions and of its role in infant-mother relationships. At any rate, diagnostic methods which fail to take this possibility into account, whether they be ingestion tests, elimination or provocative diets, or based on food diaries, will introduce false positive findings. The risk is particularly great if one accepts as allergic such commonly neurotic complaints as headache, fatigue, chilliness, and muscle discomfort. Placebo ingestion studies would seem indispensable.

Although the results presented herewith are preliminary both in nature and in number, it is hoped they will stimulate others to seek more objective means for the diagnosis of ingestant allergy. For example, even with our ingestion method, the use of flavoring and of antacids to simulate milk was not found ideal. Probably plain, powdered milk in capsules would be superior, providing desiccation can be achieved without degradation. Purified milk proteins should also be tested by the oral route, but as yet it is not practical to prepare them in amounts sufficient for the test. Our laboratory is hoping to accomplish this by use of the electrophoresis-convection apparatus of Kirkwood. It should then be feasible to reproduce the studies[10] done with cottonseed extract, where the

thresholds of susceptibility were expressed in chemical units for the skin, conjunctiva, serum, and for the oral route. There also is an urgent need to investigate the validity of Randolph's claim that headache, fatigue, and other manifestations not generally considered typical of allergy do belong in this category and are being widely misdiagnosed.

Finally, a word of caution seems in order. It would seem unwise, in view of our crude knowledge, to alarm the layman by publicizing the "dangers" attached to such common foods as milk and cereals, to say nothing of their derivatives, the sugars, starches, and oils, before confirmation by objective methods is possible. So much lay concern has been developed along this line, however, that several recent hearings were held before the United States Food and Drug Administration concerning the need to label salad dressings, bread, etc., as to their content of allergens.

CONCLUSIONS

1. A poll of 191 specialists in pediatrics or allergy revealed that 1.5 per cent of 245,000 patients were allergic to milk by clinical standards, whereas 2.3 per cent of 180,000 individuals responded to intracutaneous test.

2. An ingestion procedure was devised which called for masking of the allergen and for control feedings with placebo meals.

3. Applied to 8 patients, this approach gave promise of being superior to other diagnostic techniques in current use. Its chief asset is the exclusion of psychogenic influences from the results.

4. Intracutaneous tests with milk erred in the direction of giving false positive results, whereas protein fractions derived from milk tended toward false negative ones.

5. The need is cited for re-evaluation of the symptomatology of allergy, particularly as regards the claims of Randolph, Rinkel, and Rowe, and for the development of scientific methods of diagnosis in food allergy.

The author wishes to thank the numerous physicians who made this report possible, and to acknowledge gratefully the technical help of Miss Cecelia Spearing, Miss Ann Ryan, Miss Lillian Ingwer, and Mrs. Hazel Rice.

REFERENCES

1. Rowe, A. H.: Allergic Toxemia and Migraine Due to Food Allergy, California and West. Med. **33**: 785, 1930.
2. Rinkel, H. J.: Food Allergy. I. The Role of Food Allergy in Internal Medicine, Ann. Allergy **2**: 115, 1944.
3. Randolph, T. G.: Fatigue and Weakness of Allergic Origin, To Be Differentiated From "Nervous Fatigue" or Neurasthenia, Ann. Allergy **3**: 418, 1945.
4. Randolph, T. G.: Food Allergy, M. Clin. North America, Chicago Number **32**: 245, 1948.
5. Andreson, A. F. R.: Ulcerative Colitis, an Allergic Phenomenon, Am. J. Digest. Dis. **9**: 91, 1942.
6. Vaughan, W. T.: Practice of Allergy, ed. 2, revised by J. Harvey Black, St. Louis, 1948, The C. V. Mosby Company.
7. Lee, H. J., and Squier, T. L.: Provocative Diets in the Recognition of Food Allergy, J.A.M.A. **142**: 318-321, 1950.
8. Rinkel, H. J., Randolph, T. G., and Zeller, M.: Food Allergy, Springfield, Ill., 1950, Charles C Thomas, Publisher.
9. McMeekin, T. L., Polis, B. D., Dellamonica, E. S., and Custer, J. H.: A Crystalline Compound of β-Lactoglobulin with Dodecyl Sulfate, J. Am. Chem. Soc. **71**: 3606, 1949.
10. Loveless, M. H.: An Objective Approach to the Diagnosis of Food Allergy as Applied to Cottonseed Atopy, Ann. Allergy **8**: 15-22, 125, 1950.

ALLERGY FOR CORN AND ITS DERIVATIVES: EXPERIMENTS WITH A MASKED INGESTION TEST FOR ITS DIAGNOSIS*†

MARY HEWITT LOVELESS, NEW YORK, N. Y.

THIS symposium on food allergy is the outgrowth of recent widespread medical and lay interest aroused by claims[1,2] that cereals and also their derivative starches, syrups, sugars,[3] oils, and even their grain alcohols,[4] are important excitants of allergy. The subject entered prominently into hearings before the Federal Food and Drug Administration in 1949, when the advisability of labeling salad dressings, breads, and other edible preparations was discussed from the allergenic angle. At this time, Randolph testified that such manifestations as unexplained headache, fatigue, drowsiness, chilliness, and pulling or aching of the muscles might originate from chronic or masked allergy for such regularly ingested foods as corn, wheat, milk, and eggs.

In anticipation of these Washington hearings, the writer interviewed 19 members of the American Academy of Allergy, from various sections of the country, to learn that only 0.12 per cent of their patients were considered susceptible by clinical standards to kernel or ground corn. No convincing instance of hypersensitivity to ingested oil or sugar could be found, and only a rare case of allergy for starch—one being recalled by Spain and another by Walzer. So great was the disparity between these opinions and those of Rinkel, Randolph, and Rowe, that a search for the underlying reason was instituted. Two steps were taken. First, a canvass was made by questionnaire of specialists in allergy and pediatric allergy to gain a more considered and extensive impression of the frequency of corn allergy. Second, an objective diagnostic procedure was devised whereby individuals suspected of hypersensitivity could be subjected to standard feeding tests with whole corn and subsequently with its derivative starch and syrup. The cornstarch pudding employed for the latter could not be distinguished in appearance, taste, or texture from 2 control puddings made of cane-sweetened starch obtained from tapioca or from arrowroot. The aim was to exclude psychogenic and other extraneous factors. These "blindfold" tests were used by 11 allergists on 25 individuals who gave suggestive histories for susceptibility to corn.

MATERIAL AND METHODS

Ingestion Materials: Mush.—As a check on the validity of the history, a feeding of precooked corn-meal mush (degerminated Quaker corn meal), sweetened with "Frodex," a dried corn syrup, was advocated as a preliminary or a final step in the ingestion studies. This ready-to-serve meal was prepared, as were the puddings, by an independent manufacturer in New York City (National Starch Products Inc., to whose Mr. Vincent Marsilia and Miss Mary Bak-

*From The New York Hospital and Department of Medicine, Cornell University Medical College, New York, N. Y.

†Presented before the Sixth Annual Meeting of the Academy of Allergy, Los Angeles, Calif., on March 6-8, 1950.

kovitch the writer is very grateful for their preparation of 67 packages). The mush consisted of 13.6 Gm. of dry meal to which were added 32.1 Gm. of dried syrup containing dextrose, maltose, and such higher sugars as triose and biose. The corn meal in each feeding carried 180 mg. of protein nitrogen and the syrup added another 2.2 mg. As is the case of the puddings, this test meal was posted in a refrigerated carton to the physician just prior to the arrival of the patient, the request being made through the writer's office. Before the next feeding in the series was prepared, all details of the earlier test were in the writer's hands. Each carton was labeled with an individualized code number, so that the patient, his physician, and the author remained in ignorance as to its contents until the entire series had been completed.

The puddings each contained 10 Gm. of starch. In the case of the tapioca and the arrowroot samples, the sweetener was 20 Gm. of cane sugar, whereas 66.6 Gm. of Frodex could be incorporated into the cornstarch pudding with an equal sweetening effect. As flavoring agents, 0.3 Gm. of salt and 0.3 Gm. of citric acid were included in each pudding, 0.03 Gm. of benzoate of soda being added as preservative. When requested, synthetic wild cherry flavoring was also employed in a volume of 6 drops.

The nitrogen content of the cornstarch pudding was estimated at 4.8 mg. protein nitrogen for the starch and 4.2 mg. for the Frodex, giving a total of 9 mg. In the case of the control puddings, the content of protein in their starches being ⅓ to ⅔ that of cornstarch and the sweetener being used in smaller proportion, the total amount of protein nitrogen in the feeding was about 4.2 mg. Hence, the cornstarch meal possessed over twice the protein of the placebo meals and might have been expected, therefore, to be more allergenic if its activity were dependent on contaminating nitrogen.

Ingestion Procedure.—The routine of Rinkel and Randolph was followed as accurately as possible in its several details, corn and its derivatives being carefully excluded from the diet for at least 4 days preceding any feeding. Tapioca and arrowroot, though more rarely ingested, were also prohibited. Wherever it could be safely recommended, the patient took the suspected allergen for 4 days prior to the period of elimination. He came in fasting, was allowed to rest seated for one-half hour before the start of the experiment. All suggestive signs and symptoms were sought and recorded for the 2-hour test period, as well as for the 2-day period before and after the ingestion. The subjects were also advised to avoid, or at any rate to record, any exposure to drugs, allergens, or other factors which might color the outcome of the test.

FINDINGS

Incidence of Allergy for Whole Corn (Kernel or Meal).—Table I is based on the replies received from 56 physicians who answered the questionnaire. The data have been segregated according to the frequency with which allergy for whole corn was encountered. For 45, the incidence amounted to only 0.16 per cent, or 1 case in 600, among a population of 45,500 individuals. Five additional physicians reported 82 cases in a total of 5,200 patients, giving an incidence 10 times higher and doubling the over-all figure. Another 4 found

59 instances in 1,700, bringing the average to 0.39 per cent for a population of 52,500 subjects.

The findings of the last 4 contributors are individually listed since they differ strikingly from the others. Rinkel, for example, has published a study of 200 patients with suspected hypersensitivity for whom he diagnosed corn as the etiologic factor in 16 per cent. We have taken the liberty of multiplying this population by 5 to make it comparable with those covered by the questionnaire. The same step was taken for Randolph who reported an incidence of 20 per cent in a group of his hypersensitive subjects at the 1949 hearing before the Food and Drug Administration. Rowe's response to the questionnaire was that he encountered 25 to 30 per cent of such cases among 1,200 patients. Finally, Crandall recorded 170 instances among 565 subjects, an incidence of 30 per cent.

It will be noted that the last 4 clinicians make the diagnosis of corn allergy about 100 times more frequently than the average allergist represented by the first group. It is hoped that some possible explanations for this disparity will be found in the results of our experiments with controlled feeding, to be presented below.

TABLE I. INCIDENCE OF CLINICAL ALLERGY FOR WHOLE CORN OR CORN MEAL

				CUMULATIVE TOTALS		
ALLERGISTS	PATIENTS OBSERVED	NO. CORN-ALLERGIC	INCIDENCE (%)	PATIENTS OBSERVED	NO. CORN-ALLERGIC	INCIDENCE (%)
45*	45,573	75	0.16	45,573	75	0.16
5*	5,220	82	1.57	50,793	157	0.30
4*	1,700	59	2.88	52,493	216	0.39
Rinkel†	1,000	160	16.0	53,493	376	0.7
Randolph†	1,000	200	20.0	54,493	576	1.06
Rowe	1,200	300	25.0	55,693	876	1.57
Crandall	565	170	30.0	56,258	1,046	1.86

*Members or Fellows of the American Academy of Allergy of whom 15 were certified internists; 3 were certified pediatricians.

†From the August-September, 1949, Hearing before the Federal Food and Drug Administration.

Ingestion Studies.—Table II summarizes the findings of ingestion tests carried out on 25 individuals who gave a history suggestive of allergy for whole corn. The data have been segregated into 3 sections, depending on the clarity of the diagnosis. Group A refers to 13 individuals whose allergy seemed the most certain, confirmation of the history being found by means of ingestion tests with our standard mush meal in 5 instances, with feeding tests devised by other allergists in 5 other cases, and on the basis of convincing histories for the remaining three. Details for the experiments on all but two of the members of this group are to be found in the recorded hearings before the Food and Drug Administration of 1949 as well as in the current issue of this journal under the investigators' names.

The outcome of experiments with these 13 clear-cut instances of corn allergy can be briefly summarized in the following statements. Eleven of the subjects gave entirely negative responses to masked feedings with cornstarch. Of the 2 who reacted to the cornstarch puddings, one (JM) did so on one occasion but failed to do so during an earlier ingestion experiment. The manifestation, consisting of abdominal cramps which occurred 7 hours after the feeding, was of

moderate severity and lasted for 4 hours. The first trial had elicited only a suggestion of "gassy indigestion" after 10 hours. In contrast, the standard mush feeding had provoked marked cramps within one-half hour. Had the pudding test been reproducible, one could have accepted this as an example of cornstarch allergy, attributing the relative delay in symptoms to the lesser amount of protein in the cornstarch as compared with whole corn meal. The lack of reproducibility, however, somewhat weakens one's convictions.

The other instance of cornstarch reaction was much more convincing. Patient MB developed asthma of moderate intensity within 1 hour of receiving a pudding, later identified as containing cornstarch. After 7 days, another such pudding reproduced the manifestation in marked form and a third experiment confirmed the diagnosis of cornstarch allergy. This woman showed unmistakable reactions to whole corn meal, developing prompt contact responses of the mouth and throat as well as immediate severe asthma.

Tapioca sensitivity was noted in one of the 13 patients of Group A, the patient being MB referred to above. She experienced severe asthma within 1 hour after the masked feeding on one occasion and promptly after ingestion on another.

Arrowroot starch caused a moderately severe gastrointestinal disturbance in 1 patient, and mild asthma in another. The first subject was observed by Shulman who reported that diarrhea had occurred in 48 hours and had lasted 2 hours, after she had been given the arrowroot pudding. Rawling's patient felt somewhat nauseated at once and became mildly asthmatic within one-half hour. Both symptoms subsided quickly. The long interval involved in the first instance and the mild, transitory nature of the reaction in the second patient weaken the interpretation of these findings as evidence of allergy to arrowroot.

Of these 5 instances of response to the starch puddings, only 2 are really convincing, those of the patient, MB, who reacted to both corn and tapioca. If so few cases are to be found among a group of patients of such highly selective character, the incidence must indeed be low among the general population. The suitability of the 13 individuals in Group A for the feeding experiments with cornstarch is made evident by their unequivocal clinical sensitivity toward whole corn. Table II reveals that 5 of them developed marked asthma, 7 various degrees of gastrointestinal disturbance, 8 nasal manifestations of allergy, 2 urticaria or atopic eczema, and 1 marked headache. With the possible exception of the latter, all these are classical expressions of allergy. Furthermore, they occurred promptly after the cereal had been eaten, 9 being noted within one-half hour and the rest within 5 hours. Although headache is a borderline manifestation, in the case of Sheldon's patient it was evoked in 30 minutes and was of extreme severity, so that it could be accepted as presumably allergic in origin.

Concerning the other derivatives of corn, none of the 11 individuals tested with syrup, sugar, or oil gave any sign of untoward effect, even on repeated feedings. One patient was also negative to the intravenous administration of dextrose. The involvement of cane sugar can be excluded from consideration since each of the several subjects responding to 1 starch pudding was fully tolerant of the other pudding which contained the same sweetener. This also applies to the flavoring and preservative used in all puddings.

TABLE II. INGESTION RESPONSES TO WHOLE CORN, CORNSTARCH, SUGAR, SYRUP, AND OIL IN PATIENTS SUSPECTED OF HAVING CORN ALLERGY

		RESPONSE TO INGESTION OF WHOLE CORN							RESPONSE TO STARCHES & CORN PRODUCTS					
			SYMPTOMS					ONSET						
PHYSICIAN	PATIENT	BASIS OF DIAGNOSIS	ASTHMA	G.I.	NASAL	SKIN	HEADACHE	IN HRS. P.C.	CORN-STARCH	TAPIOCA	ARROW-ROOT	CORN SYRUP	CORN SUGAR	CORN OIL
Group A: 13 Patients With Excellent Ingestion Result and/or History for Corn Allergy														
Sheldon	1*	Trial		++	++			½	0			0	0	0
Sheldon	2*	Trial			++		+++	½	0			0		0
Sheldon	3*	History	+++					½	0			0		
Sheldon	4*	Trial		+	+			¼	0,0			0		
Sheldon	5*	History		+++	++			¾	0			0	0	
Sheldon	6*	History			+++			1	0			0	0	0
Rawling	1*	Trial	+++		+ eye			3	0†		0†		0	0
Cazort	KEP†	Mush†		+++		+		¼	0†	0†	0†	0	0	0
Halpin	CH*	Trial	+++	+++		+++		¼	0†				0 i.v.	0
									0†		0†	0	0	
Bernton	2*MB	Mush†	+++					¼	+++†	+++†	0†	0	0	0
									+++†	+++†			0	0
									+++†				0	
Conn	JK	Mush†			+++			5	0†	0†	±†			
Shulman	JM	Mush†		+++				½	±†					
									++†	0†	++†			
Rawling	2	Mush†	+++	+	+			½	0†		+†		0	0
Total	13	5 Trial 5 Mush†	5	7	8	2	1	¼-5	2 pos.	1	2	9 neg.	8 neg.	8 neg.
Group B: 10 Patients With Fair Ingestion Result and/or History for Corn Allergy														
Bernton	1*	Mush†			+				0†					
Lazar	PB	Mush†	+++					6	0†	0†	0†			
Black	CB	Mush†	++					12	0†	0†	+†			
Altose	BC	Mush†	+		+			3½	++†	±†	±†			
Altose	JS	Mush†			++	++		24	+++†	+†	0†			
									+++†					
Cazort	LO	History	+++	++				chronic	0†	0†	0†			
Cazort	MCK	History	+++			++			0†	0†	0†			
Cazort	RU*	History	+++	+++				2-3	0	0	0	0		0
Cazort	AR	Starch History?	+++			+++		12	+++†					
Black	WBC	History				++		12	0†	±†	±†			
Total	10	5 Mush†	7	2	3	4		2-24	3	1	1			
Group C: 2 Patients With Possible History but Negative Ingestion Test														
Loveless	AN	Mush†	0				0		+†	++†	++†			
										0	0			
Loveless	AHR	Mush†					±		++†	±†	±†			
									0†					
									0†					
Grand Total	25	12 Mush† 5 Trial	12	9	11	6	1	¼-24	7	3	4	10 neg.	8 neg.	9 neg.

These findings confirmed the claims of Rinkel and Randolph and the observations of Walzer and Spain that cornstarch can act as an ingestant allergen, rather to the surprise of the investigating physicians. The starches of tapioca and probably also of arrowroot can play a similar role. The convincing example found in Bernton's patient can be examined in detail in the August-September hearings of the Food and Drug Administration for 1949 and seen in synoptic form in Table III.

TABLE III. INGESTION STUDIES ON ASTHMATIC PATIENT, MB (BERNTON)

MATERIAL INGESTED	AMOUNT FED (GM.)	NO. OF TRIALS	ASTHMA INDUCED	INTERVAL IN MIN.
Corn meal*	13.6	1	+++	several
Dextrose	12.0	3	0	
Cornstarch*	10.0	3	++,+++	3 - 55
Corn oil	30.0	2	0	
Corn syrup	30.0	2	0	
Arrowroot starch*	10.0	3	0	
Potato starch*	10.0	1	0	
Tapioca starch*	10.0	2	+++	15 - 55

*Loveless standard pudding or mush.

The failure of most patients in this group of definite whole corn sensitivity to react to cornstarch can be demonstrated by the case of Halpin. This 27-year-old woman gave a history of immediate edema of lips and tongue as the result of ingesting kernel and ground corn on 2 occasions. Severe urticaria, dyspnea, cough, and wheeze shortly developed and were followed by diarrhea and collapse which required 3 administrations of epinephrine for their control. The standard mush feeding was contraindicated in this severe case. The subject submitted to pudding tests with cornstarch on 2 occasions and with arrowroot on 1, and remained symptom-free. She not only tolerated ingestions of corn syrup, corn oil, and corn sugar but also took the latter by vein equally well. These findings are summarized in Table IV.

The young college student, KE, of Cazort is another example of extreme hypersensitivity toward kernel corn in combination with complete tolerance for large doses of each derivative by mouth. In keeping with his history, mush provoked immediate "tingling, burning, and a thick feeling in the mouth and throat." Severe abdominal cramps and urticaria were present some hours later. On the contrary, no untoward effects followed the taking of masked puddings in which the starches of corn, tapioca, or arrowroot were present. Similarly, corn oil, syrup, and sugar were taken in masked form without incident.

Six other individuals gave equally convincing results when tested by Sheldon with his own types of masked feeding. All these clearly corn-reactive patients proved to be fully tolerant of the starch and syrup of corn, and those given corn sugar and oil were similarly negative. Patient 1, investigated by Rawling with his own method of trial feeding with whole corn, like that of Conn who employed our standard mush, is an acceptable member for Group A in spite of the somewhat delayed appearance of manifestations. Both individuals were given cornstarch pudding, as well as 1 or more control puddings, without significant effect.

TABLE IV. INGESTION STUDIES ON PATIENT C. BY DR. HALPIN

DATE	PRECEDING SYMPTOMS	MATERIAL INGESTED	SYMPTOMS				
			ASTHMA	NAUSEA	DIARRHEA	URTICARIA	EDEMA
1946	0	Corn bread†	onset +++ ¼ hr.	+++	+++	+++ ¼ hr.	+++*
		Corn on cob†	+++ ¼ hr.	+++	+++	+++ ¼ hr.	
1948	0	Glucose 10 % intravenously	0	0	0	0	0
		Corn oil	0	0	0	0	0
		Corn sugar	0	0	0	0	0
		Corn syrup	0	0	0	0	0
7/27/49	0	Cornstarch	0	0	0	0	0
1/10/50	0	Cornstarch	0	0	0	0	0
6/29/49	0	Arrowroot	0	0	0	0	0

*Lips and tongue.
†Small portion of a serving.

TABLE V. INGESTION STUDIES ON PATIENT AN

DATE	PRECEDING SYMPTOMS	MATERIAL INGESTED	SYMPTOMS							
			ASTHMA		HEADACHE		FATIGUE		VERTIGO	
				HRS.P.C.		HRS.P.C.		HRS.P.C.		HRS.P.C.
11/23/49										
10:30	0	Mush*	±	¾ - 1¼	0		0		0	
12:40	0 for 1 hr.	Corn on cob	±	¼ - 2¼	0		0		0	
11/18/49	0	Corn starch*	+	1 - 5	0		+++	½ - 4½	++	5½ - 6
11/9/49	Fatigue ++	Arrowroot*	++	5 -	0		0		0	
12/2/49	0	Tapioca*	++	1 - 2½	0		0		0	
1/31 /50	0	Tapioca	0		0		0		0	
2/3/50	0	Arrowroot crackers	0		+++	¼ - ½	0		0	
2/8/50 10:00	Asthma ±	Saline 1 c.c.	+	½ - 1¾	+	¼ - 1¾	0		0	
11:45	Asthma ±	Saline 1 c.c.	+	½ -	+++	5 min. - 1	+	1 -	0	

*Loveless standard test meal.

When these 2 experiments are included with those described above for Group A, it is apparent that the large proportion of patients clearly susceptible to whole corn is unquestionably tolerant of its derivative starches and sugars, this being the observation for 11, and possibly 12, of the 13 test subjects.

Group B furnishes less valuable evidence because in general its responses to ingested corn were either mild in degree or delayed in development. Five of its members were diagnosed by ingestion test with our standard mush, whereas the history alone was used as the basis for diagnosis for the other 5. In spite of these shortcomings, some weight may be placed on the negative responses of 7 of the subjects to cornstarch and to such other corn derivatives as were employed. The anomalous situation encountered in the experiments with 2 of the patients, who appeared more reactive to starch than to meal, is worthy of further investigation. The third case listed as positive for cornstarch by the pudding test is difficult to interpret both from the viewpoint of the feeding result and the history. This 30-month-old baby (AR) was suspected of being cornstarch-allergic by its mother and was known to be reactive to both corn and cottonseed flours by inhalation. The only ingestion experiment done was one with cornstarch pudding. Three hours later a few hives had developed on the knee, and by 12 hours the eruption was generalized and mild asthma was present. The latter became so severe by the next morning that the child was hospitalized. It was unfortunate that control and whole corn ingestion studies were refused after this development.

Group C was composed of 2 of the author's patients who deserve brief mention because their symptoms resembled those classed as allergic by Randolph but not generally accepted as such by the profession. These responses were elicited by the derivatives but not by whole corn.

Table V summarizes the findings with An, a woman who was having asthma almost daily which was considered to be caused by several danders, house dust, and foods. After her first ingestion test with arrowroot pudding, she suffered an attack of moderately severe asthma. Nine days later the ingestion of cornstarch pudding was shortly followed by marked fatigue and mild asthma. After their disappearance some 4 hours later, a short spell of vertigo was noted. Her subsequent examination with standard mush and fresh kernel corn failed to duplicate these manifestations aside from a suggestion of mild asthma, which was surprising in view of the fact that larger doses of the hypothetical allergens in corn must have been involved. Interpretation of this woman's reactions was again made difficult by her failure to develop, at home, symptoms of asthma which followed the taking of tapioca in the office. Furthermore, arrowroot appeared to elicit asthma of moderate severity 5 hours after she ate a masked pudding under our observation but when she tried arrowroot crackers at home a severe, brief headache was the result. Suspecting by now that factors other than our test meal allergens were operative, we subjected her to a feeding experiment with saline solution which she believed to be an allergenic extract. This gave rise to mild asthma by 30 minutes and to headache almost immediately. Fatigue of slight degree was also reported. Without the repeated tests and the saline control, this woman would have been considered allergic to all 3 of the starch puddings, especially if the diagnosis had been guided by the criteria of Rinkel and Randolph.

For comparable reasons, one might have been misled by the initial cornstarch reaction of AH. His persistent fatigue was increased as also was his headache by this masked pudding test. Repetition of the ingestion in 2 weeks yielded a negative result except for a suspicion of fatigue. Still a third experiment provoked no complaints whatsoever. These 2 essentially negative responses to cornstarch are consistent with his tolerance of both mush and kernel corn. It was important to the understanding of this case that repeat tests be carried out.

DISCUSSION

A survey of 56 allergists and pediatric allergists throughout the country revealed that for all but a few physicians clinical allergy for whole corn is a rarity which is encountered 100 times less frequently than Rinkel, Randolph, Rowe, and Crandall have reported. Some explanations for this disparity have been uncovered by our experiments with objective feeding tests. It was found that extraneous factors, especially of psychologic origin, can complicate the diagnosis unless the patient is subjected to repeated studies, to masked ingestions, and to placebo meals.

Whereas no evidence was found for the allergenicity of corn oil, syrup, or sugar, clinical reactions were, to our surprise, encountered following the controlled ingestion of the several starches employed for these studies. The clinical significance of this type of hypersensitivity would not appear, however, to have the practical importance assigned to it by Randolph and his school. For one thing, its occurrence was rare even among our group of patients who were selected on the basis of their marked allergy for whole corn and who were tested with relatively huge ingestant doses of starch. Randolph has claimed that provocative amounts of starch allergen escape from paper cartons into milk, sauerkraut, and frozen foods. It seems unlikely that our cornstarch-reactive cases would have been affected by such traces. At any rate, the incidence of clinical susceptibility ought to be far lower with such small amounts of this substance than with the 10 Gm. of cornstarch involved in our puddings.

Presumably any allergenicity of starch, syrups, and sugars would be referable to contaminating proteins carried along from the whole cereal into the derivatives. Starch itself would probably not be antigenic in view of its prompt breakdown into smaller molecular substances by enzymes present in all biologic fluids. Furthermore, the proteins of whole corn would also be reduced considerably in activity because of the drastic treatment involved in the preparation of the derivatives, including heating and strong acidification.

Theoretically, bacteria might play a role in contributing antigens to corn derivatives. It is known, for example, that *B. macerans* is introduced during the preparatory process. In addition, it might be found that this organism, like the streptococcus, can synthesize dextrans, which have been shown to possess immunological activity.[5] Before any of these thories can be accepted, it will be necessary to support them by controlled experimental evidence.

It would seem that the chief cause of the disagreement among allergists concerning the frequency of food allergy must relate to the diagnostic criteria employed. The individual feeding procedures of Rinkel and Randolph, as well as

the elimination diets of Rowe, were introduced because the cutaneous test was found to be unreliable in this type of hypersensitivity. Although they constitute a step in the right direction, these methods fail to take into account the influence of extraneous factors, particularly those of psychologic origin. Consequently, an abnormally high incidence of positive results would be expected. Furthermore, there has recently been added to the diagnostic list a considerable variety of new symptoms. Although such an increase in the scope of allergy may eventually be found justifiable, this can only be decided after a scientific diagnostic procedure has been devised. To attempt to set up a new method simultaneously with the introduction of new symptomatology is tantamount to testing the validity of one unknown by the use of another. There is, then, an urgent need at the moment for the creation of an adequate diagnostic technique. The adequacy should be firmly established by its application to only those patients whose diagnosis is unequivocal. The members of Group A fulfilled this requirement in the "blindfold" ingestion procedure described in this article, their diagnoses resting on the speed and classical form of their reactions to whole corn. It is true that the psychologic factor was not excluded due to the impossibility of masking the characteristic taste and appearance of the unrefined cereal. However, the mush feeding was only a screening technique to confirm a straightforward history, and the psychologic factor was effectively controlled in the masked ingestion procedure associated with the pudding tests for starch and sugar allergy.

SUMMARY

1. A poll of allergists revealed that clinical symptoms from ingested corn were encountered in only 0.16 per cent of their 45,000 patients. This stands in marked contrast to an incidence of 16 to 30 per cent reported by Rinkel, Randolph, Rowe, and Crandall.

2. "Blindfold" ingestion studies associated with placebo meals were done in 25 patients with histories suggestive of corn allergy. A few instances of reaction to large feedings of the starches of corn, tapioca, and arrowroot were encountered, but no case of susceptibility for corn syrup, sugar, or oil. The symptoms of several patients were found to be psychogenic rather than due to the suspected food.

3. An appeal is made for the introduction of controlled, objective methods to the study of food allergy.

The writer wishes to thank the physicians who cooperated to make this study possible, and to acknowledge aid of Misses C. Spearing and A. Ryan as well as Mrs. H. Rice.

REFERENCES

1. Rinkel, H. J., Randolph, T. G., and Zeller, M.: Food Allergy, Springfield, Ill., 1950, Charles C Thomas, Publisher.
2. Rowe, A. H.: Elimination Diets and the Patient's Allergies, Philadelphia, 1944, Lea & Febiger.
3. Randolph, T. G., Rollins, J. P., and Walter, C. K.: Allergic Reactions Following the Intravenous Injection of Corn Sugar (Dextrose or Glucose), J. Lab. & Clin. Med. **34**: 1741, 1949.
4. Randolph, T. G.: Concepts of Food Allergy Important in Specific Diagnosis, J. ALLERGY **21**: 471, 1950.
5. Hehre, E. J., and Neill, J. M.: Formation of Serologically Reactive Dextrans by Streptococci from Subacute Bacterial Endocarditis, J. Exper. Med. **83**: 147, 1946.

CLINICAL EXPERIENCE IN CORN SENSITIVITY*

KARL D. FIGLEY, M.D., AND FRANK F. A. RAWLING, M.D., TOLEDO, OHIO

FOOD allergy is a clinical reality responsible for allergic rhinitis, asthma, urticaria, atopic dermatitis, and less frequently, headache and gastrointestinal symptoms. In our experience, it is hazardous to recognize other symptoms as being on this basis unless accompanied by one of the major allergic manifestations. This viewpoint then limits somewhat our selection of patients to undergo study and may be responsible for the variance of opinions that we are observing.

By far the majority of adult patients presenting respiratory symptoms are found to be allergic to inhalants, the control of which leads to a remarkable simplification of what appeared to be a complicated situation. When food is found to be a factor, the common offenders are milk, eggs, or wheat. We rarely see multiple food sensitivities in an individual patient.

With this as a background, for the past 2 years or so we have searched for corn sensitivity. Diagnosis is based upon one or more of these findings: history, positive skin test with whole corn meal extract, or the ability to reproduce symptoms by ingestion of unrefined corn by the patient who has been adequately prepared. By this, we mean rigid avoidance of all sources of corn in the diet for 4 days, followed on the morning of the fifth day by the ingestion of corn meal.

We have found only 3 patients in whom allergic symptoms could be produced by trial ingestion of whole corn: asthma in 2 cases, and urticarial swelling of the tongue and throat in a third. However, in the latter case, symptoms appeared only when the patient ate large quantities of corn meal on 3 successive days; the trial ingestion of a single dose had no effect. The 2 asthmatics both developed asthma after trial ingestion of whole corn, and the history of each clearly demonstrates their sensitivity to this food. However, in neither did trial ingestion of cornstarch, sugar, or oil produce symptoms.

This was demonstrated in these 2 cases by trial ingestion of puddings, the content of which was unknown to us at the time of testing. The patients were prepared by 4 days of rigid avoidance of all known sources of corn and its products. One patient developed no reaction whatever to any of the puddings or to corn oil. The other developed asthma one-half hour after eating the pudding that was made of arrowroot starch and contained no corn products. He showed no reaction to cornstarch. Furthermore, both remained well by simple avoidance of whole corn, along with appropriate control of inhalant factors. The patient who developed urticaria was under treatment for asthma, but the ingestion of corn had no effect upon this symptom. He showed a strongly positive scratch test to corn. One asthmatic gave a slightly positive skin test, while the other has never shown any reaction.

*Read before the Sixth Annual Meeting of the American Academy of Allergy, Los Angeles, Calif., March 6-8, 1950.

We found 8 cases in which the only evidence of corn sensitivity was a positive skin test. In 7 of these, either by history or trial insufflation, it could be shown that the sensitivity was limited to corn when contacted as an inhalant, and there was no evidence of its activity as an ingestant.

On the basis of these few cases, one can draw no definite conclusions. As pointed out, our experience is limited to those patients having well-recognized allergic symptoms. Hence, we do not have referred to us for study many patients with symptoms such as gastrointestinal difficulties, muscular aching, uncomplicated fatigue, or headaches. However, within the borders of our territory, we find little evidence of corn sensitivity, and have never had a patient clinically sensitive to refined corn products. This is in agreement with our opinion regarding food allergy in general. Sensitivity to refined food products from any source does not present a clinical problem either from a diagnostic or therapeutic viewpoint. We concur heartily with Lee and Squier[1] in their stand that misguided and extreme measures of specific food avoidance are unnecessary.

REFERENCE

1. Lee, Howard J., and Squier, Theodore L.: Provocative Diets in the Recognition of Food Allergy, J. A. M. A. **142**: 318, 1950.

CLINICAL EXPERIENCE WITH OBJECTIVE DIAGNOSTIC TESTS IN CORN SENSITIVITY

ALAN G. CAZORT, M.D., LITTLE ROCK, ARK.

AT MY request Dr. Loveless sent the 3 starch puddings described in her paper* containing cornstarch, arrowroot and tapioca, but identified only with code numbers, A-1, F-1, and E-1, respectively, and also 1 of corn meal, to 5 patients presumed on the evidence given in the case reports below to be clinically sensitive to corn antigen. Each of these patients reacted on scratch test with corn meal extract with a wheal 15 mm. or greater transverse to the starch.

Each patient was instructed to eat one of the starch puddings at midmorning on successive days, or at longer intervals, after a breakfast consisting only of usual foods, and was warned against any unusual activity for several hours afterward. Symptoms or signs observed during the next several hours were to be noted and reported to me. Neither the patients nor I knew the contents of the respective puddings, except the obvious corn meal.

CASE 1.—J.R.L., 82 years old, an attorney, was first seen in St. Vincent's Infirmary in July, 1949, wearing an oxygen mask because of severe dyspnea. His son stated that he had had asthma for over 20 years, and chronic indigestion even longer. He knew that dust from livestock feed had formerly caused paroxysmal sneezing, but had had no exposure for years. The present attack of asthma had been severe and continuous for 3 months.

Physical examination revealed no evidence of circulatory impairment nor sinus infection. The only significant findings, except a rather poor nutritional state, were those typical of bronchial asthma. The response to 5 minims (0.3 ml.) of epinephrine 1-1000 was dramatic.

Scratch tests to all cereals were strongly positive. He had been eating corn and wheat daily. On a cereal-free diet he was able to leave the hospital on the third day. He has eaten no cereal and has had no dyspnea since.

He ate the 3 starch puddings without symptoms, but preferred not to try the corn meal.

He is now 83, has gained 25 pounds since July, 1949, practices his profession, and recently made a trip to Chicago alone.

CASE 2.—B.K., a medical student on whom experiments were reported in the International Correspondence Club of Allergy, ate all the 4 puddings. He reported: A-1 (cornstarch) no symptoms; E-1 (tapioca) and F-1 (arrowroot) followed immediately by mild nausea which he attributed to the physical properties of the puddings. The corn meal, however, caused the usual symptoms of "tingling, burning, and a thick feeling" in the mouth and throat almost immediately. That evening he had severe cramping in his abdomen, along with urticaria.

CASE 3.—C.A., 30 months old, known to be sensitive to corn and to cottonseed by inhalation and suspected by his mother of being sensitive to corn starch by ingestion, ate A-1 (cornstarch) at 9:00 A.M. By noon he was having some urticaria about the knees. At 9:00 P.M. the urticariae were general and asthma was noted. Before morning he had severe asthma and was taken to the hospital. The parents refused to try E-1 and F-1. This was the only severe asthma the boy had had since his original examination in January, 1949. Previously he had been hospitalized repeatedly because of it, and I think we may consider this episode a response to the corn starch. A scratch test with corn starch paste produced a definite but not an irregular wheal 3 mm. across with 15 mm. of erythema.

*Contained in this issue (p. 500).

CASE 4.—D.McK., 3 years old, with severe asthma and atopic dermatitis, showed only moderate to doubtful improvement for several months after avoiding house dust and excluding corn and wheat from his diet, having reacted by scratch test to all of these. An unusually severe attack of asthma with aggravation of the rash followed a known exposure to flour and corn meal in the kitchen. This suggested he was absorbing cereal antigens by inhalation. All home baking was stopped 4 month ago, and he has had very little trouble. He ate the 3 starch puddings without symptoms. On my advice the corn meal was not given.

CASE 5.—J.R., a 4-year-old asthmatic, was known to be sensitive to corn by ingestion when brought to me some 2 years ago. He too reacted with whealing to a scratch test with moist corn meal. He has eaten corn starch pudding, corn oil, and Karo on numerous trials without symptoms.

He had no symptoms from the few teaspoonsful of the 3 starch puddings which his mother could persuade him to take. He has eaten much greater quantities of starch in the past, however, without symptoms. Against my advice the mother tried to feed him the corn meal pudding and although he ate 2 teaspoonsful of it he had no ill effect. A few nights later, however, he was given canned green corn for dinner. That night he had severe asthma with vomiting, which persisted for 2 days.

CONCLUSIONS

These observations suggest:

1. That the clinical allergic reaction is quantitative as well as qualitative.
2. That corn starch does not contain enough antigen to affect most corn-sensitive patients when eaten in the usual quantities.
3. That corn starch does contain some corn antigen to which extremely sensitive individuals may react from ingestion.

FOOD ALLERGY: ACUTE VS. CHRONIC*†

JOHN H. MITCHELL, M.D., COLUMBUS, OHIO, AND JESS GAMBLE, M.D., HOUSTON, TEXAS

ALLERGIC reactions to foods are characteristically acute and transient. From the history the experienced physician can usually suspect the cause and readily reproduce the symptoms by clinical trial with the disguised food. The patient himself is often aware of the cause, particularly when attacks have been recurrent. Scratch tests are usually positive and avoidance of the offending food results in prompt relief within a few hours. This, then, is the typical pattern of food allergy.

However, syndromes such as perennial vasomotor rhinitis, perennial "intrinsic" asthma, chronic urticaria, atopic dermatitis, and chronic gastrointestinal disorders simulate clinically the acute allergic disorders due to extrinsic allergens but present disturbing variations such as confusing histories, negative skin tests, equivocal results following clinical trial with undisguised allergens, and most important of all, chronicity.

Over the years efforts have been made to include the atypical disorders within the allergic hypothesis, and many theories have been advanced to reconcile the obvious inconsistencies. Sincere attempts by many allergists to integrate these theories with clinical experience have been disappointing. Although the concept of acute allergic reactions to food is universally accepted, the hypothesis of chronic food allergy leaves much to be explained. It is most difficult to be certain that chronic or delayed manifestations can be induced by exposure to disguised foods.

Elimination diets[3] and the leucopenic index,[5] with various modifications, have been advocated as useful means to a solution of these problem cases. More recently, a quantitative increase in a constellation of events[2] such as sneezing, coughing, increasing fatigue, and muscular aching, has been recommended as a diagnostic criterion of chronic food allergy.

If the theory of chronic or "masked" food allergy is valid it seems likely that similar changes should be observable following the deliberate induction of an acute allergic reaction to food. Therefore, the following experiment was done:

L. Q., a 31-year-old man, an asthmatic, clinically and skin-sensitive to cottonseed, ingested cottonseed protein in gradually increasing amounts until asthma was induced. Serial blood counts were made at frequent intervals before, during, and after the attack. No significant variation in the circulating leucocytes was observed. Fig. 1 graphically summarizes the experiment.

*From the Department of Medicine, Ohio State University College of Medicine, Columbus, Ohio.

†Presented at the Sixth Annual Meeting of the American Academy of Allergy, Los Angeles, Calif., March 6-8, 1950.

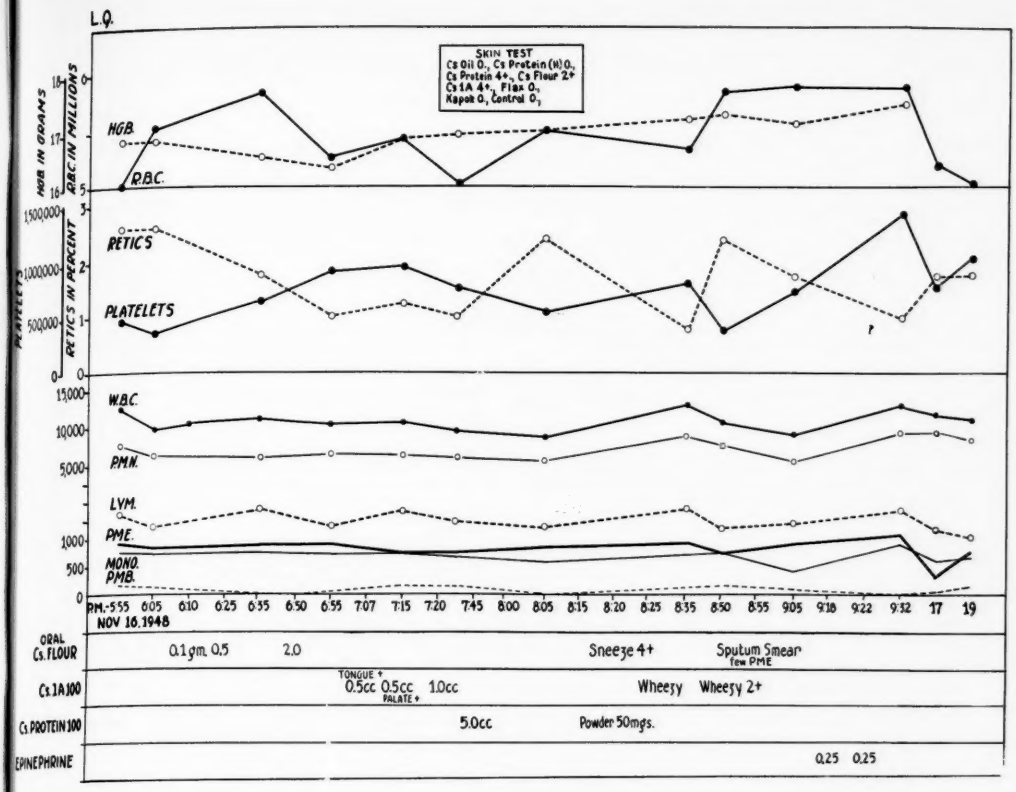
L.Q.
SKIN TEST
Cs Oil 0., Cs Protein (H) 0.,
Cs Protein 4+, Cs Flour 2+
Cs 1A 4+, Flax 0.,
Kapok 0, Control 0,
HGB. IN GRAMS
R.B.C. IN MILLIONS
HGB.
R.B.C.
RETICS IN PERCENT
PLATELETS
RETICS
PLATELETS
W.B.C.
PMN.
LYM.
PME.
MONO.
PMB.
P.M.-5.55 6.05 6.10 6.25 6.35 6.50 6.55 7.07 7.15 7.20 7.45 8.00 8.05 8.15 8.20 8.25 8.35 8.50 8.55 9.05 9.18 9.22 9.32 17 19
NOV 16.1948
ORAL Cs. FLOUR
0.1 gm. 0.5
2.0
Sneeze 4+
Sputum Smear few PME
Cs 1A 100
TONGUE + 0.5cc 0.5cc PALATE +
1.0cc
Wheezy
Wheezy 2+
Cs PROTEIN 100
5.0cc
Powder 50mgs.
EPINEPHRINE
0.25 0.25

Fig. 1.

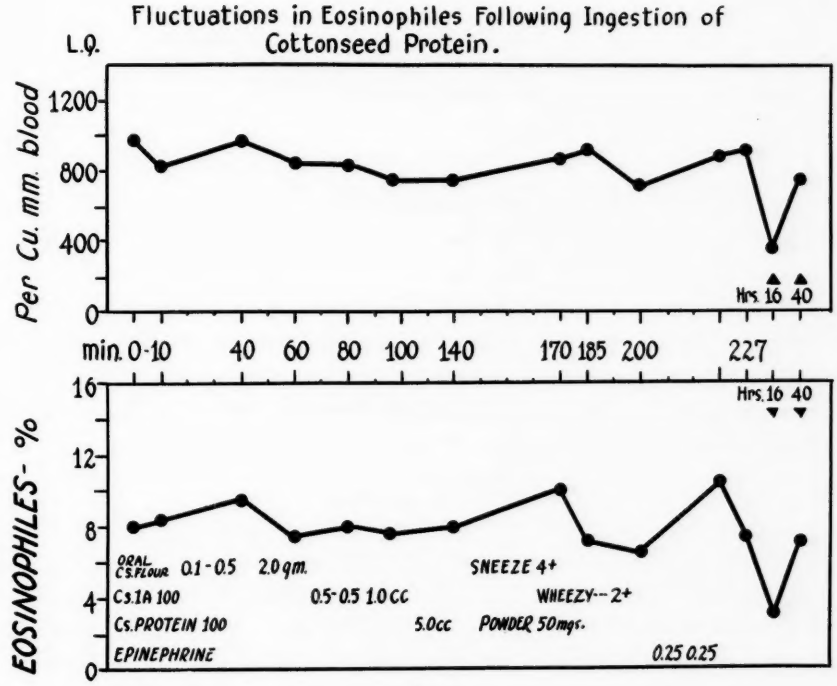
Fluctuations in Eosinophiles Following Ingestion of Cottonseed Protein.
L.Q.
Per Cu. mm. blood
Hrs. 16 40
min. 0-10 40 60 80 100 140 170 185 200 227
EOSINOPHILES - %
ORAL CS. FLOUR 0.1-0.5 2.0 gm.
SNEEZE 4+
Cs 1A 100
0.5-0.5 1.0 CC
WHEEZY -- 2+
Cs. PROTEIN 100
5.0cc
POWDER 50 mgs.
EPINEPHRINE
0.25 0.25

Fig. 2.

Fig. 2 has been prepared on a scale to exaggerate eosinophile fluctuations. With the onset of wheezing (185 minutes) there was a slight decrease in eosinophiles; then a slight increase (227 minutes) after the injection of epinephrine 1:1000, 0.25 c.c. × 2 for the control of asthma. These variations were not of sufficient magnitude to be considered of diagnostic significance. The patient had received immunizing inoculations of cottonseed protein extract for several years and had developed considerable tolerance. In fact, it was quite

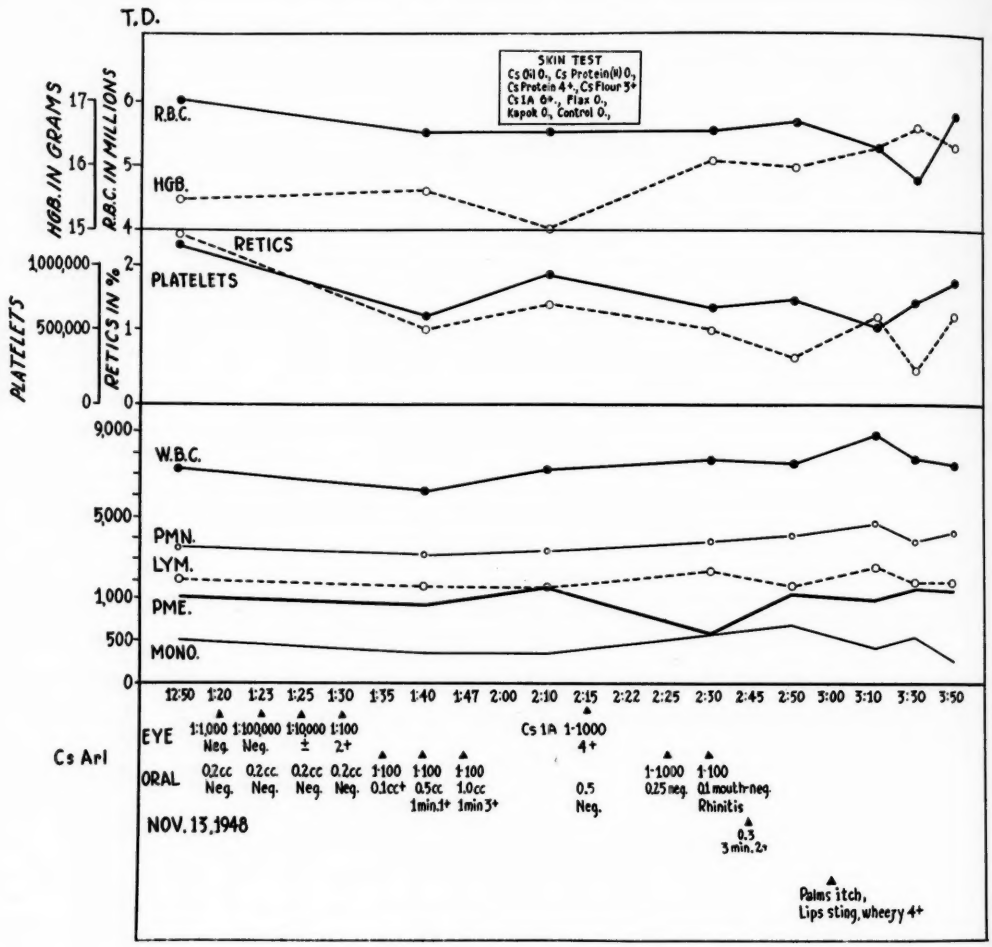
T.D.
SKIN TEST
Cs Oil 0., Cs Protein(N) 0.,
Cs Protein 4+, Cs Flour 3+
Cs 1A 6+, Flax 0.,
Kapok 0., Control 0.,
HGB. IN GRAMS
R.B.C. IN MILLIONS
R.B.C.
HGB.
RETICS
PLATELETS
RETICS IN %
PLATELETS
W.B.C.
PMN.
LYM.
PME.
MONO.
12:50 1:20 1:23 1:25 1:30 1:35 1:40 1:47 2:00 2:10 2:15 2:22 2:25 2:30 2:45 2:50 3:00 3:10 3:30 3:50
EYE
1:1,000 Neg. 1:100,000 Neg. 1:10000 ± 1:100 2+ Cs 1A 1-1000 4+
Cs Arl
ORAL
0.2cc Neg. 0.2cc. Neg. 0.2cc Neg. 0.2cc Neg. 1:100 0.1cc+ 1:100 0.5cc 1min.1+ 1:100 1.0cc 1min 3+ 0.5 Neg. 1-1000 0.25 neg. 1:100 0.1 mouth-neg. Rhinitis 0.3 3 min. 2+
NOV. 13, 1948
Palms itch, Lips sting, wheezy 4+

Fig. 3.

a surprise to observe the amount of cottonseed protein he could ingest in aqueous solution. Finally a 50 mg. vial of powder was emptied onto his tongue. Immediately he began to sneeze and within a few minutes was definitely asthmatic. From the rapidity of the reaction it was assumed the powder had been inhaled. So actually, this attack was not induced by ingestion but rather by inhalation of the allergen. Of particular interest, however

was the count taken 14 hours after the onset of asthma showing a decrease of over 50 per cent eosinophiles, due probably to the epinephrine effect. At the next count made 48 hours later, there was a return to the base line.

A similar experiment was repeated in the case of T. D., a 34-year-old man, also a cottonseed-sensitive asthmatic; the results are summarized in Fig. 3. Asthma was induced using liquid preparations of the allergen so that there was no chance for inhalation. Here again, there was insufficient fluctuation in the total leucocytes or in the eosinophiles to be considered diagnostically significant. Fig. 4 gives a high-power magnification of the eosinophile curve.

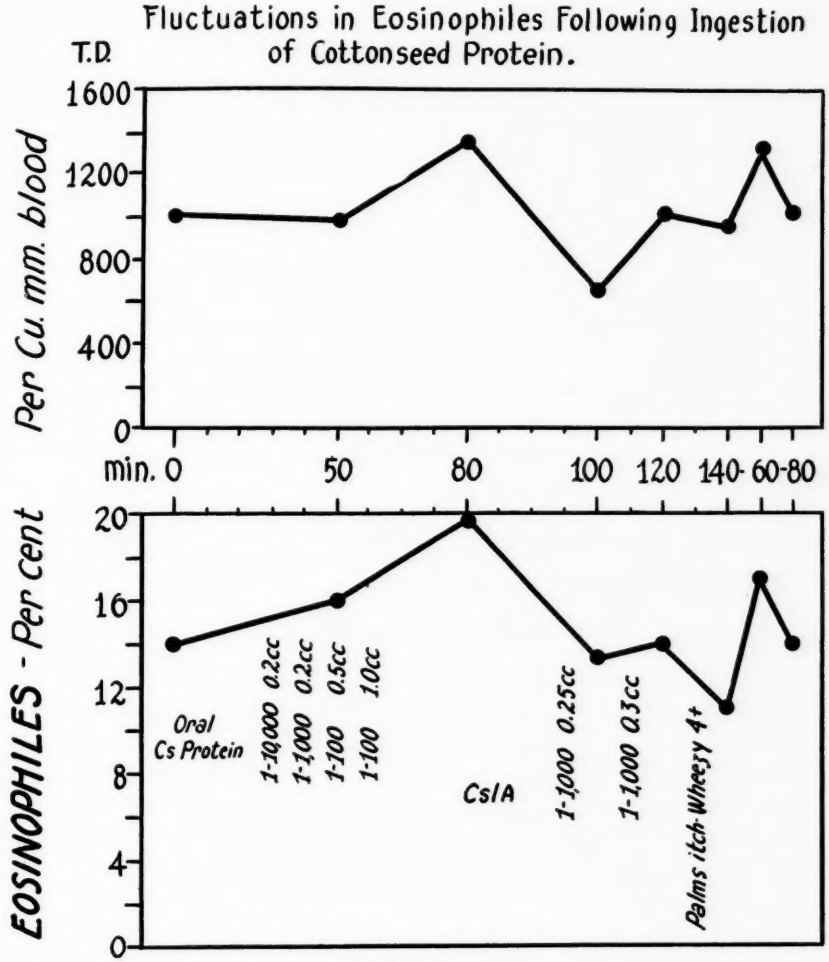

Fig. 4.

Unfortunately this man was not asked to return on subsequent days for further counts. At the time these studies were made, interest centered in the immediate effects of the acute allergic reaction to the allergens rather than the delayed effects of epinephrine described by Thorn.[4]

In addition to blood counts, clinical observations were made; no increase in sneezing or coughing was observed nor was there any mention by the patient of fatigue or muscular aching during the 3-hour period previous to the development of wheezing. Patients had not been warned to be on the lookout for these symptoms; the observer merely made notes of what he saw.

Results of similar studies of 2 patients,[1] where asthma was induced by subcutaneous administration of cottonseed protein, conform with those reported here. There was a surprising stability of the eosinophiles in spite of severe constitutional reactions. The total leucocytes increased sharply immediately following necessary injections of epinephrine but did not fluctuate when the drug could be withheld.

CONCLUSIONS

1. Serial blood studies and observations of minor symptoms appear to be of little aid in anticipating the onset of asthma deliberately induced by the ingestion of cottonseed protein.

2. The circulating eosinophiles did not fluctuate significantly before, during, or immediately after the constitutional reaction.

3. The validity of the theory of chronic or "masked" food allergy is questioned.

The author wishes to express sincerest appreciation to Charles A. Doan, M.D., for his helpful suggestions and for making available the facilities of the hematology laboratory, Ohio State University, College of Medicine, and to Georgia E. Gwinner, M.T., for her technical assistance.

REFERENCES

1. Mitchell, John H.: Fluctuations in Circulating Eosinophiles During Induced Asthma, Ann. Allergy, to be published.
2. Randolph, Theron G.: Food Allergy, Medical Clinics of North America, January, 1948.
3. Rowe, Albert H.: Elimination Diets and the Patient's Allergies, Philadelphia, 1944, Lea & Febiger.
4. Thorn, George W.: Adrenal Insufficiency, Springfield, Ill., 1949, Charles C Thomas, Publisher.
5. Vaughn, Warren T.: Leukopoenic Index, J. Lab. & Clin. Med. **21**: 1278, 1936.

Original Articles

REAGIC SERUM FRACTIONS OBTAINED BY THE ELECTROPHORESIS-CONVECTION METHOD*†‡

DAN H. CAMPBELL, PH.D., JOHN R. CANN, PH.D., PASADENA, CALIF.,
TOWNSEND B. FRIEDMAN, M.D., CHICAGO, ILL., AND
RAYMOND A. BROWN, PH.D., PASADENA, CALIF.

DEVELOPMENT of the electrophoresis-convection technique as described by Nielsen and Kirkwood[1] has made available the fractionation of complex mixtures such as the antigens of ragweed reported by Loveless and Best[2] and the fractionation of serums as reported by Cann, Brown, and Kirkwood.[3] The fractions obtained are dependent to a large extent on electrophoretic mobility but the method has the practical advantage over the classical Tiselius method in that the entire amount of a relatively large sample can be fractionated. Since this method makes use of relatively small differences in mobility and isoelectric points, a finer separation can be obtained than with the use of the Tiselius apparatus. At the time this work was carried out the techniques of operating the electrophoresis-convection apparatus had not yet been refined to the point where the electrophoretic constituents of serum could be separated in a state of high purity in a single stage of operation. Of course, subsequent stages of fractionation would have served to purify these initial serum fractions. However, that was not warranted in the study since separation in a single stage of operation was sufficiently efficient to allow valid correlation to be made between the constituents of the proteins and biological activity. For example, only one or two electrophoretic components predominate in any given fraction so that biological activity can easily be correlated with the presence or absence of a limited number of components.

Studies of the reagic activity of electrophoretic fractions from allergy serum have been made by Newell, Sterling, Axman, Burden, and Krejci,[4] in which fractions were removed from the Tiselius cell. These authors concluded that reagic activity resided in the gamma components. However, since the amount of material obtained by such a method is too limited to permit analysis of electrophoretic purity or to study serological properties of such fractions, a program of fractionation by electrophoresis-convection methods was started. The following report describes the fractionation of two reagic serums and the subsequent electrophoretic and reagic properties of each fraction. Studies have actually been made on seven such serums but because some of the serological characterization has not been completed the entire study will be published later.

*Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, Calif., and Children's Memorial and Michael Reese Hospitals, Chicago, Ill.

†This work was supported in part by a grant from the United States Public Health Service.

‡Read before the Sixth Annual Meeting of the American Academy of Allergy, Los Angeles, Calif., March 6-8, 1950.

The Fractionation of Serum.—Two 70 ml. samples of each serum were simultaneously fractionated in two separate cells and the respective fractions combined at the termination of the experiment. The fractionation was carried out in such a manner that the original serum was separated into two fractions, referred to as top and bottom, which indicated their respective positions in the separation chamber. The top fraction was taken off and the bottom refractionated. The second bottom preparation was then refractionated by the addition of one volume of saturated ammonium sulfate into albumin and remaining globulin. The final preparations were dialyzed against 0.9 per cent NaCl solution, the protein concentration determined by Nessler's reactions and adjusted to 0.7 per cent protein. This amount was an arbitrary value based on the maximum concentration that could be obtained for some of the fractions.

The two serums reported here are given in Table I as M I and TF III. The first was obtained from a person whose history indicated a sensitivity only to egg. Subsequent tests of egg white fractions, Miller and Campbell,[6] indicated that his sensitivity involved chiefly ovomucin. This was not known at the time the fractions were tested and standard egg white antigen was used in the Prausnitz-Küstner tests. The second (serum TF III) was from a patient who showed multiple sensitivity including cottonseed which was used in the test reactions.

TABLE I. SOME CHARACTERISTICS OF FRACTIONS FROM REAGIC SERUMS

FRACTION	COMPONENTS AND RELATIVE CONCENTRATION PER CENT					
	ALBUMIN 5.7-6.5	α_1 5.6-4.2	α_2 4.1-3.6	β 3.5-3.8	γ 2.0-0.8	P K TITER*
Serum M I Egg-sensitive only						
Original serum	61	5	8	14	12	1:10
T76	7	0	4	16	73	0
T78	11	0	8	18	64	0
β78	63	6	9	22	0	0
BA78	88	4	4	4	0	0
BG78	27	7	47	19	0	1:20
Serum TF III Multiple Sensitivity (Cottonseed-tested)						
Original serum	65	5	12	8	10	1:10
T69	7	0	0	13	80	1:10
T70	13	4	8	14	61	1:20
β70	68	5	21	5	0	1:10
BA70	83	10	7	0	0	0
BG70	10	15	46	20	9	1:50

*Titer based on dilution of a 0.7 per cent solution of protein.

Test for Reagic Activity.—The protein solutions were sterilized by filtration through a washed Seitz filter and injected intradermally in varying dilutions of 0.05 ml. volumes. Seventy-two hours later the prepared sites were tested by intradermal injections of antigen. Positive tests were indicated by definite wheal and erythema.

RESULTS

The electrophoretic pattern of each fraction was determined and the mobility and relative concentration of each component was calculated from enlarged electrophoretic diagrams according to the method of Pedersen.[5] The

classification of components according to their mobility range into albumin, α_1-, α_2-, β- and γ globulin is somewhat empirical in some instances but the approximate positions are obvious. The data pertaining to the electrophoretic composition and reagic activity of each fraction is given in Table I. The M I serum gave a passive transfer in a 1:10 dilution and all the fractions except the last (BG78) were inactive. Since practically all the γ globulin was in the first two top fractions (T76 and T78) it would appear as though, in this particular serum at least, that the reagin occurred in the other serum globulins. Although the major component of the BG78 fraction was α_2-globulin, the analysis of the electrophoretic data is not quantitative enough to eliminate the possibility that β-globulin contains reagin. However, one can rule out γ globulins with a fair degree of certainty. The second serum (TF III) did not show the same limitation of reagic activity. In fact, all but the BA70 fraction, which was mostly albumin, showed about the same degree of activity.

These experiments as well as others which will be reported later, indicated that reagins do not occur predominately in the γ globulin component, and in most serums from patients showing sensitivity to a single antigen the reagic activity may be limited to the electrophoretic components having mobilities characteristic of α- or β-globulins. It was also of interest to note that specific blood group agglutinins and in one instance, typhoid agglutinins, were associated with the γ component as would be expected from previous work.

SUMMARY

1. The fractionation of serums from allergic individuals has been accomplished by electrophoresis-convection methods.

2. Prausnitz-Küstner tests on the resulting fractions indicated that reagic activity was closely associated with the α- and β-globulins, particularly in simple sensitivities and that activity occurred in all the globulins in multisensitivity.

The authors are particularly indebted to Mrs. Said for technical assistance in the electrophoresis analyses.

REFERENCES

1. Nielsen, L. E., and Kirkwood, J. G.: Fractionation of Proteins by Electrophoresis-Convection, J. Am. Chem. Soc. **68**: 181, 1946.
2. Loveless, M. H., and Best, R.: Allergenic Fraction of Ragweed Pollen Prepared by Electrophoresis-Convection (Nielsen-Kirkwood Cell), Federation Proc. **8**: 407, 1949.
3. Cann, J. R., Brown, R. A., and Kirkwood, J. G.: The Fractionation of Bovine Serum Proteins by Electrophoresis-Convection, J. Am. Chem. Soc. **71**: 1609, 1949.
4. Newell, J. M., Sterling, A., Axman, M. F., Burden, S., and Krejci, L. E.: Electrophoretic Separation of Antibody From Human Allergic Serum, J. ALLERGY **10**: 513, 1939.
5. Pedersen, K. O.: *in* The Ultracentrifuge, T. Svedberg and K. O. Pedersen, London, 1940, Oxford University Press, p. 296.
6. Miller, H., and Campbell, D. H.: Skin Test Reactions to Various Chemical Fractions of Egg White and Their Possible Clinical Significance, J. ALLERGY **21**: 522, 1950.

SKIN TEST REACTIONS TO VARIOUS CHEMICAL FRACTIONS OF EGG WHITE AND THEIR POSSIBLE CLINICAL SIGNIFICANCE*†‡

HYMAN MILLER, M.D., BEVERLY HILLS, CALIF., AND DAN H. CAMPBELL, PH.D., PASADENA, CALIF.

AS A result of studies[1] on the serological reaction between ovalbumin and reagin from egg-sensitive patients, it became obvious that failures to obtain serological reactions with ovalbumin were due to the lack of the reagin to ovalbumin in many serums. Consequently, it was of general interest and of specific importance to our own studies to obtain some idea as to what reagins were usually present in egg-sensitive patients reacting to egg white. We selected 3 different preparations of egg white and 4 chemical fractions which were carefully purified. These 4 fractions were selected because good methods have been devised for their purification and they have been fairly well characterized. There are probably more antigenic substances in egg white as the following data indicate but a relative idea of reaginic activity may be obtained from the following study.

MATERIALS AND METHODS

Test Antigens.—Five different antigenic materials were tested, namely, egg white, ovalbumin, ovomucin, lysozyme, and trypsin inhibitor. They were all made up in 1.0 per cent solutions in standard buffer pH and sterilized with a Seitz filter. These materials were used undiluted in performing all puncture tests and were diluted to 0.1 per cent with normal saline containing 1:20,000 Merthiolate for all intradermal tests. Intradermal tests were done with each antigen only when less than a 3 plus reaction was obtained on puncture test.

Three different preparations of egg white were used. These consisted of a commercial egg white allergen, fresh egg white diluted to 1.0 per cent protein, and lyophiled egg white made up in buffer to 1.0 per cent protein. Since no essential difference in skin reactivity between the 3 preparations was noted, they are not listed separately in the table.

The ovalbumin was obtained in crystalline form from fresh egg white and recrystallized 4 times according to the method of Kekwick and Cannon.[2] The material was electrophoretically homogeneous.

The ovomucin was also prepared from fresh egg white in a manner similar to that described by Sørensen.[3] The water-soluble ovomucin fraction isolated from the salt-precipitated globulin-mucin mixture was finally purified by precipitation with acetic acid at pH 4.0 and heated to 80° C. for one hour. The resulting solution was then centrifuged at about 40,000 g. for 30 minutes and lyophiled. The product showed one major electrophoretic component of

*From the Allergy Service of the Los Angeles County General Hospital; the Department of Allergy, University of Southern California Medical School; the Allergy Service of Wadsworth General Hospital, U.S.V.A., and the Gates and Crellin Laboratories of Chemistry, California Institute of Technology (Contribution No. 1397).

†Read before the Sixth Annual Meeting of the American Academy of Allergy, Los Angeles, Calif., March 6-8, 1950.

‡This work was supported in part by a grant from the Rockefeller Foundation.

low mobility and a trace (2.0 per cent) of a fast component at pH 7.3. Although there was no evidence of positive charged materials at this pH, the possibility of contamination with other materials including lysozyme cannot be excluded.

The lysozyme was prepared in a crystalline form according to the method of Alderton, Ward, and Fevold[4] and lyophiled. Electrophoretic patterns of the final product in barbital buffer pH 8.6 indicated one major positive charged component with closely associated irregularities that may have been anomalies due to buffer activity or impurities.

The preparation and properties of the trypsin* inhibitor have been described by Lineweaver and Murray.[5] No further treatment or characterization was made. This substance has been classified as a mucoid.

Clinical Tests.—A total of 342 persons were tested by puncture and intradermal methods. No particular age group, sex, or clinical syndrome was selected. Most were patients with symptoms of allergy and with positive skin reactions to some allergens. Only a part of the group gave clinical histories of egg sensitivity. Fifty-eight per cent failed to give skin reactions to any of the egg antigens.

RESULTS

The results of tests on the reacting subjects have been tabulated (Table I) according to antigen and per cent of subjects reacting to the various possible combinations of the 5 antigens. Although the original data on the skin reactions were expressed as 1 plus . . . 4 plus, the 1 plus reactions have been ignored because of possible doubtful significance. When reactions of 2 plus or greater are considered, the total reactors were 140 and of these only 74 included lysozyme antigen since it was not available at the first part of the program.

TABLE I. SUMMARY OF SKIN REACTIONS TO EGG WHITE ANTIGENS*

PER CENT REACTIONS TO POSSIBLE ANTIGEN COMBINATIONS OF:					
NONE (%)	ONE (%)	TWO (%)	THREE (%)	FOUR (%)	FIVE (%)
58	W 13.3	WA 1.4	WAM 4.2	WAML 7.7	34.0
	A 2.8	WM 6.3	WAL 0.7	WAMT 4.0	
	M 3.5	WL 4.2	WAT 2.7	WALT 2.7	
	L 6.2	WT 1.3	WML 10.5	AMLT 5.4	
	T 1.3	AM 0	WMT 1.3		
		AL 0.7	WLT 4.0		
		AT 0	AML 2.1		
		ML 5.6	AMT 1.3		
		MT 4.0	ALT 0		
		LT 4.0	MLT 1.3		

*W = egg white.
A = ovalbumin.
M = ovomucin.
L = lysozyme.
T = trypsin inhibitor.

A total of 38 subjects reacted to only a single antigen, 33 to 2, 33 to 3, 21 to 4, and 25 to all 5 preparations. The group reacting to egg white but no

*The trypsin inhibitor was kindly supplied by Dr. Lineweaver of the Western Regional Laboratory.

other fractions was unexpectedly large (13.3 per cent) This result indicates that egg white includes some antigen not present in the fractions used (e.g., conalbumin) and perhaps materials not yet described. The number of other reactions to single antigens were much less and occurred in the order of lysozyme > ovumucin > albumin > trypsin inhibitor. Those not reacting to egg white but to isolated components indicate that insufficient quantities of these preparations were present in the whole egg white. As might be expected, the various combinations of positive reactions reflect, to some extent, the initial number to single antigens. Hence, combinations containing egg white, lysozyme, and ovomucin tend to increase the number of reactants and albumin and trypsin inhibitor tend to decrease the number with one exception. This occurred when albumin was added to the egg white, ovomucin, lysozyme (WML 10.5 per cent) group and the number was markedly increased (WAML 7.7 per cent). No particular combination seemed to be unusually active and lack of sufficient number hardly justifies a statistical treatment. Reactions to all the components seem to be the predominant combination, but the fact that about 60 per cent do not indicates that sensitization to the antigenic components of a complex mixture such as egg white is dependent upon individual variation rather than the nature of the antigen.

SUMMARY

1. Skin tests on egg-sensitive individuals with egg white and 4 components (albumin, ovomucin, lysozyme, and trypsin inhibitor) indicates that sensitization often occurs to only a few and in some instances to only one of the components.

2. It is, therefore, important from a clinical standpoint to recognize the possibility that sensitization may occur to antigens which are not present in sufficient quantities in the crude extracts to give positive skin tests.

REFERENCES

1. Miller, H., and Campbell, D. H.: Reagins. Preliminary Report on Experimental Evidence in Support of a New Theory of Their Nature, Ann. Allergy **5**: 236, 1947.
2. Kekwick, R. A., and Cannon, R. K.: The Hydrogen Ion Dissociation Curve of Crystalline Albumin of Hen's Egg, Biochem. J. **30**: 227, 1936.
3. Sørensen, M.: Kohlenhydratgehalt der Proteine des Hühneneiweiss, Biochem. Ztschr. **269**: 271, 1934.
4. Alderston, G., Ward, W. R., and Fevold, H. L.: Isolation of Lysozyme From Egg White, J. Biol. Chem. **157**: 43, 1945.
5. Lineweaver, H., and Murray, C. W.: Identification of Trypsin Inhibitor of Egg White With Oromucoid, J. Biol. Chem. **171**: 568, 1947.

EFFECT OF SLOWLY ABSORBING ANTIGEN (RAGWEED) ON NEUTRALIZING ANTIBODY TITER*†

SAUL MALKIEL, M.D., AND SAMUEL M. FEINBERG, M.D., CHICAGO, ILL.

ANTIGEN extracts which are prepared with the objective of delaying their absorption and prolonging their stay in the body might possess certain advantages in clinical therapy. Any or all of the following goals might be achieved: lesser likelihood of constitutional reactions, radical reduction in the number of injections, and more effective immunization because of a more continuous stimulation of antibody formation. Over a period of years many such preparations have been tried in this laboratory, and while some of them had varying degrees of desirable features, none of them were completely satisfactory. The preparations having the greatest possibilities for delay in absorption were, as a rule, also the most irritating to the tissues. In addition, the literature includes the efforts of many investigators.

The application of alum-precipitated pollen extract to human therapy was investigated by Zoss, Koch, and Hirose,[1] Sledge,[2] and Stull, Cooke, Sherman, Hebald, and Hampton.[3] The use of a lanolin-olive oil preparation and, subsequently, a tannic acid precipitate of pollen extract had been advocated by Naterman.[4-6] Spain, Fuchs, and Strauss[7, 8] claimed favorable results with pollen extract dissolved in gelatin. Rockwell[9] used an insoluble "pollen hydrochloride" while Stull et al.[3] prepared formalin-treated, heat-treated, irradiated, and acetylated extracts. That the ideal preparation is still to be achieved, however, is apparent in that none of these desensitization techniques have been widely accepted.

Our interest was again stimulated by the observation of the progress which has attended the prolongation of penicillin absorption and maintenance in the blood stream since the original Romansky[10] formula was promulgated. It was for this reason that we reopened our investigations using an oil-aluminum monostearate depot.

EXPERIMENTAL

Preparation of extract.—The usual 3 per cent weight/volume saline extract of 50-50 mixed ragweed pollen was lyophilized, solubilized starch to a 6 per cent concentration having been added as a binder. The dried residue was incorporated into sesame oil containing 2 per cent aluminum monostearate in dilutions which were compatible with therapeutic treatment. Chlorobutanol was added to a 0.5 per cent concentration.

Active anaphylaxis.—Two individual series of guinea pigs, consisting of 8 and 35 animals, respectively, were injected intraperitoneally with 1.0 ml. of a 3 per cent ragweed-oil preparation. Two identical series of animals were

*From the Department of Internal Medicine, Division of Allergy and Allergy Research Laboratory, Northwestern University Medical School, Chicago, Ill.

†Presented at the annual meeting of the American Academy of Allergy, Los Angeles, Calif., March 6, 1950.

injected similarly with 1.0 ml. of a 3 per cent saline-ragweed extract for controls. At irregular intervals, 2 or 5 animals of each respective group and the corresponding controls were challenged by injecting 1 ml. of the 3 per cent saline-ragweed extract intravenously.

Determination of delay in absorption.—Two nonallergic human beings were injected subcutaneously in the upper arm in the region of the deltoid muscle with 1.0 ml. of 3 per cent ragweed-oil preparation. At irregular intervals during the ensuing 48 hours, samples of blood were withdrawn from each of the subjects, under sterile conditions, the blood allowed to coagulate, and the sera stored at 4° C. As controls, a second pair of volunteers were injected with 1.0 ml. of 3 per cent saline-ragweed extract and blood samples were similarly withdrawn.

The presence of circulating ragweed allergen in each sample of serum was determined by its reagin-neutralizing capacity. An equal volume of each serum was mixed individually with diluted stock reagin obtained from a patient who had never received desensitization treatment. Five-hundredths of a ml. of each mixture was used to passively sensitize a local site of skin on the forearm of nonallergic individuals. After 48 hours the sites were challenged by a single subcutaneous injection of 0.5 ml. of 3 per cent saline-ragweed extract administered in the region of the deltoid muscle. The reactions produced at each sensitized site were determined subjectively by recording the time when itching was first observed by the subject and objectively by recording the degree of erythema and wheal formation at each site after given periods of time.

The stock reagin was found to be just neutralized when one volume, diluted 1:2, was mixed with one volume of saline-ragweed extract, diluted 1:1,000,000, as determined by the passive transfer technique.

Desensitization therapy.—Patients were selected who gave positive skin reactions, scratch or intradermal, to ragweed extract. The course of therapy, which was that usually employed for desensitization, consisted of weekly injections, starting with very dilute solutions, the size of the subsequent dose being determined by each patient's individual local reaction. It was felt desirable to increase the concentration of the doses as rapidly as possible. A record of the clinical symptoms was kept throughout the course of therapy. Samples of blood were withdrawn preceding the start of the therapy and again towards the end of the ragweed season. These sera were titrated for the presence of neutralizing antibody. Sera were obtained from 3 patients receiving concomitant saline-ragweed extract therapy.

Determination of neutralizing antibody.—The sera collected were all heated at 56° C. for 1 hour in order to inactivate reagin. To two volumes of each serum serially diluted 1:2, there was added one volume of a predetermined concentration (1:200,000) of saline-ragweed extract. After incubation at 37° C. for about 30 minutes, one volume of undiluted reaginic serum was added and these mixtures used for local passive sensitization on the forearms of nonallergic individuals. Challenge of the sites after 48 hours was performed by injecting

0.3 ml. of 3 per cent saline-ragweed extract into the upper arm. Adequate controls were maintained and the reactions at the local sites observed both subjectively and objectively.

RESULTS

The results of active anaphylaxis are shown in Table I. There is no apparent difference in the sensitizing capacity between the oil-ragweed preparation and the saline-ragweed extract. No information concerning the relative rate of absorption of the preparations can be ascertained by this experiment although at the end of 42 days the oil-ragweed treated animals seemed to be slightly more sensitive.

TABLE I. GUINEA PIGS CHALLENGED WITH 1 ML. AQUEOUS RAGWEED EXTRACT, I.V., AFTER SENSITIZATION WITH 1 ML., I.P.

DAYS AFTER SENSITIZATION	AQUEOUS RAGWEED EXTRACT	RAGWEED-OIL PREPARATION
7 days	±	±
	-	-
	±	-
	+	±
	±	-
11 days	+ ±	± ±
	+ ±	- ±
	±	±
	++	++
	++	++
15 days	++	++
	++	++
16 days	+++	++
	+	+++
	++	+
	++±	++±
	+++	+++
21 days	+	+
	+	+
	++++	++
	+	++
	+	++++
24 days	+++	++
	++	+
	++	+++
	+	+++
	+	+++
25 days	++	+++
	++	+++
31 days	+	+
	+++	+
	+	+++
	+	++
	±	+++
39 days	±	++++
	+	
42 days	+	++++
	++	±
	±	±
	+	++++
	+++	++++

Anaphylactic reactions range from ±, mild, to ++++, death.

Incorporation of the ragweed extract into oil causes a prolongation of absorption. The results, in Table II, indicate that absorption of ragweed allergen from the oil-ragweed preparation is prolonged approximately three times that of the saline extract as measured by the presence of circulating allergen in the serum. Measurable allergen appears in the serum at about the same time in each case. Although there is an eventual disappearance of allergen with both preparations, allergen undoubtedly is present in amounts too small to be detected by the method used. However, since these comparisons are relative, it is evident that allergen from the oil-ragweed preparation remains in the serum for some time compared to that from the saline-ragweed extract which disappears or, at least, cannot be detected.

TABLE II. TITRATION FOR PRESENCE OF CIRCULATING RAGWEED ALLERGEN
CHALLENGE DOSE, 0.5 ML. AQUEOUS RAGWEED EXTRACT
48 HRS. AFTER PASSIVE SENSITIZATION OF SKIN SITES

	SKIN SITES SENSITIZED WITH EQUAL VOLUME REAGINIC SERUM AND SERUM FROM SUBJECTS TREATED WITH			
	AQUEOUS RAGWEED EXTRACT		RAGWEED-OIL PREPARATION	
TIME AFTER CHALLENGE DOSE	PATIENT W. T. D.	PATIENT E. E.	PATIENT C. R. C.	PATIENT V. E. C.
0	+++	+++	+++	+++
37 min.				-
1 hr. 2 min.			-	
1 hr. 42 min.		+		
1 hr. 50 min.	+			-
2 hr. 40 min.		+	-	
2 hr. 50 min.				-
3 hr. 38 min.			-	
3 hr. 50 min.	+	+		-
4 hr. 42 min.				-
5 hr. 21 min.		+		
5 hr. 38 min.			±	
6 hr. 50 min.	++	++±		
7 hr. 50 min.	++±			
19 hr. 50 min.				±
20 hr. 47 min.			±	
22 hr. 02 min.		++±		
22 hr. 20 min.	+++			
24 hr. 39 min.			±	
27 hr. 50 min.				++
30 hr.		+++		
30 hr. 44 min.	+++			
46 hr. 17 min.				+++
47 hr. 43 min.			+++	
47 hr. 51 min.		+++		
48 hr. 27 min.	+++			

The clinical results were for the most part unsatisfactory. Of the patients treated, both pre- and post-treatment serum was obtained from only 17. The amelioration of clinical symptoms was relatively negligible. Several of the patients reported some improvement or "better this year." It should be stated that the patients were selected at random without regard to past history as far as severity of hay fever or previous therapy was concerned. It should also be noted that the ragweed pollinosis season in this area (Chicago) for 1949 was relatively severe. The neutralizing antibody titer and other pertinent data

appear in Table III. It can be seen that there was about a fourfold rise in the neutralizing antibody titer following treatment. This rise is relatively insignificant from a clinical viewpoint although the increase in antibody content is significant. It is interesting to note that on at least two occasions constitutional reactions were obtained within 5 minutes following a desensitizing dose. The neutralizing antibody titers of 3 patients concomitantly treated with the usual saline-ragweed extract were not significantly higher than those of the experimental group.

TABLE III

PATIENT	NO. OF TREATMENTS	MAX. DOSE GIVEN		NEUTRALIZING ANTIBODY TITER		CLINICAL RESULTS EXCERPTS
				BEFORE	AFTER	
		ML.	DILUTION	TREATMENT		
G. B.	11	0.30	1:1000	1:32	1:128	Considerable hay fever and asthma
D. J. D.	18	0.75	1:1000	1:64	1:512	Hay fever symptoms worse
H. Du. P.	12	0.35	1:1000	1:64	1:1024	Hay fever at height of season
R. G.	17	0.20	1:100	1:32	1:512	Asthma during season
H. D. H.	16	0.35	1:100	1:32	1:1024	Better than 1948
J. J. H.	15	0.20	1:1000	1:32	1:1024	Had asthma during season
J. R. H.	9	0.85	1:1000	1:128	>1:1024	No improvement
D. M.	7	0.70	1:10 000	1:128	>1:1024	Sneezing
J. J. K.	16	0.70	1:1000	1:8	1:256	Better this year
M. M.	10	0.15	1:100	1:16	1:1024	Worse than previous years
A. G. M.	17	0.20	1:100	1:8	1:1024	Much better
M. Me.	15	0.50	1:1000	1:32	1:1024	Sneezing and wheezing
E. F. O.	12	0.65	1:10,000	1:128	1:1024	Mild asthma, August
M. S.	10	0.10	1:100	1:16	1:512	Hay fever and some asthma
R. J. T.	18	0.50	1:100	1:64	>1:1024	Inconclusive
R. W. T.	12	0.50	1:100	1:128	>1:1024	Much better this year
A. J. W.	12	0.40	1:1000	1:64	>1:1024	Better this year

DISCUSSION

Theoretically, certain objectives are to be expected by the deposition of a slowly absorbed antigen in the tissues. A reduction in the number of injections ought to be a possibility, a diminution in the constitutional reactions should be expected, and a more complete immunity might be attained by the maintenance of a high antibody level by virtue of continuous antigenic stimulation.

None of these objectives were defined by these experiments. Since these experiments were at this time of the trial-and-error variety, there being no past experience with this vehicle available, the series of injections administered followed the usual mode of therapy, i.e., weekly injections. No attempt, therefore, was made to reduce the number of injections. In view of the fact that the clinical results were discouraging, it seems unlikely that the latter procedure would produce a greater symptomatic effect. That constitutional reactions can be avoided by an antigen with a moderately slowed absorption has not been found to be the case. From experiments on nonallergic subjects and the constitutional reactions which did occur in the course of treatment it can be con-

cluded that at least a significant amount of allergen is picked up by the circulation in a relatively short time. If a more complete immunity means that symptoms are diminished, then this objective, too, has not been accomplished. However, there did appear an increase in the neutralizing antibody titer which seems to be significant immunologically. It should be stated that these conclusions are the result of a therapy which was started too late for remarkable results even if the therapy were orthodox in that relatively few injections were given. This is hardly a defense of the results, for, whatever the conclusions, it is apparent that this particular preparation falls short of the goal.

The results which have been obtained are much too meager to afford much evidence concerning the role of the neutralizing antibody in clinical immunity. It should be emphasized that since its demonstration[11-15] the presence of neutralizing antibody has been associated with minimizing the severity of the reagin-allergen reaction and giving the patient comparative freedom from symptoms. Although Loveless[16, 17] believes that the neutralizing antibody is a measure of clinical immunity, Cooke[18] entertains a reasonable doubt supported by the results of Gelfand and Frank[19] and Alexander, Johnson, and Bukantz.[20] These results substantiate those of others[19, 20] that therapy with ragweed extract causes an increase in neutralizing antibody in the allergic and nonallergic individual.[21] More than this cannot be deduced from the available data, for the clinical results were not striking in either direction.

SUMMARY

1. A sesame oil-aluminum monostearate preparation of ragweed extract has been shown to prolong the absorption of the allergen.

2. Therapy with this preparation results in an increased titer of neutralizing antibody.

3. The results are insufficient to draw any conclusions regarding the relationship between neutralizing antibody and clinical results.

We are indebted to the Abbott Laboratories, North Chicago, Ill., for the actual preparations and to Dr. Israel A. Fond of the Veterans Administration for the carrying out of some of the clinical therapy.

REFERENCES

1. Zoss, A. R., Koch, C. A., and Hirose, R. S.: Alum-ragweed Precipitate: Preparation and Clinical Investigation; Preliminary Report, J. ALLERGY **8**: 329, 1937.
2. Sledge, R. F.: Treatment of Hay Fever With Alum-precipitated Pollen Extract, U. S. Nav. M. Bull. **36**: 18, 1948.
3. Stull, A., Cooke, R. A., Sherman, W. B., Hebald, S., and Hampton, S. F.: Experimental and Clinical Study of Fresh and Modified Pollen Extracts, J. ALLERGY **11**: 439, 1940.
4. Naterman, H. L.: The Treatment of Hay Fever by Injections of Pollen Extract Emulsified in Lanolin and Olive Oil: A Preliminary Report, New England J. Med. **218**: 797, 1938.
5. Naterman, H. L.: The Treatment of Hay Fever by Injections of Suspended Pollen Tannate, J. ALLERGY **12**: 378, 1941.
6. Naterman, H. L.: The Effect of Zinc on the Stability of Pollen Tannate, J. ALLERGY **13**: 385, 1942.
7. Spain, W. C., Fuchs, A. M., and Strauss, M. B.: A Slowly Absorbed Gelatin-Pollen Extract for the Treatment of Hay Fever, J. ALLERGY **12**: 365, 1941.
8. Spain, W. C., Fuchs, A. M., and Strauss, M. B.: The Treatment of Hay Fever With Gelatin-Pollen Extracts, J. ALLERGY **14**: 376, 1943.

9. Rockwell, G. E.: Preparation of a Slowly Absorbed Pollen Antigen, Ohio State M. J. **37**: 651, 1941.
10. Romansky, M. J., and Rittman, G. E.: A Method of Prolonging the Action of Penicillin, Science **100**: 196, 1944.
11. Cooke, R. A., Barnard, J. H., Hebald, S., and Stull, A.: Serological Evidence of Immunity With Coexisting Sensitization in Type of Human Allergy (Hay Fever), J. Exper. Med. **62**: 733, 1935.
12. Sherman, W. B., Stull, A., and Cooke, R. A.: Serologic Changes in Hay Fever Cases Treated Over a Period of Years, J. ALLERGY **11**: 225, 1940.
13. Loveless, M. H.: Immunological Studies of Pollinosis: I. The Presence of Two Antibodies Related to the Same Pollen Antigen in the Serum of Treated Hay-Fever Patients, J. Immunol. **38**: 25, 1940.
14. Loveless, M. H.: Humoral Antibody and Tissue Tolerance Induced in Pollen-Sensitive Individuals by Specific Therapy: A Preliminary Report, South. M. J. **33**: 869, 1940.
15. Scully, M. A., and Rackemann, F. M.: Studies on the Blocking Antibody of Cooke in the Treatment of Hay Fever, J. ALLERGY **12**: 549, 1941.
16. Loveless, M. H.: Immunological Studies of Pollinosis. IV. The Relationship Between Thermostable Antibody in the Circulation and Clinical Immunity, J. Immunol. **47**: 105, 1943.
17. Loveless, M. H.: Immunologic Studies of Pollinosis. VI. Shortening the Treatment of Hay Fever, J. ALLERGY **15**: 311, 1944.
18. Cooke, R. A.: A Consideration of Some Allergy Problems. II. Serologic Studies of the Skin-reacting Allergies, J. ALLERGY **15**: 212, 1944.
19. Gelfand, H. H., and Frank, D. E.: Studies on the Blocking Antibody in Serum of Ragweed-treated Patients. II. Its Relation to Clinical Results, J. ALLERGY **15**: 332, 1944.
20. Alexander, H. L., Johnson, M. C., and Bukantz, S. C.: Studies on Correlation Between Symptoms of Ragweed Hay Fever and Titer of Thermostable Antibody, J. ALLERGY **19**: 1, 1948.
21. Loveless, M. H.: Immunological Studies of Pollinosis. III. Fluctuations in Antibody-Titer of Normal Individuals Subcutaneously and Intravenously With Pollen Extract Over Protracted Periods, J. Immunol. **44**: 1, 1942.

COMPLEMENT FIXATION STUDIES IN ALLERGY*

PHILIP A. CAVELTI, M.D.,† LOS ANGELES, CALIF.

ALTHOUGH skin-sensitizing antibodies can usually be demonstrated in the serum of individuals with atopic allergy by the Prausnitz-Küstner method of passive transfer, it is common knowledge that such serum, as a rule, fails to produce a reaction in precipitin tests with allergenic extracts (pollen, epidermals, etc.) or by other in vitro methods including the collodion particle technique.[1, 2] On the other hand, positive results by means of complement fixation reactions have been described by several workers. Walker[3] studied the complement fixing properties of serum from asthmatic patients in the presence of various allergens such as extracts of horse dander, cat hair, and wheat. Positive reactions, occurring with antigen dilutions varying from 1:100 to 1:10,000,000, were observed in a portion of the patients while skin tests were positive in most of them. Walker also noted that the complement fixation reaction became negative upon specific hyposensitization. Gyoergy, Moro, and Witebsky[4] found that the serum from eczematous infants fixed complement in the presence of egg white in most cases where the passive transfer reaction to egg white was positive. The use of active patients' sera and of the human complement contained therein usually gave better results than inactivated serum plus guinea pig complement. While the sera of egg-sensitive individuals reacted only with high antigen dilutions (1:100,000 to 1:1,000,000), anti-egg white sera produced artificially in rabbits or in healthy children did not show this prozone; they reacted with low dilutions of the antigen as well as with higher ones. The latter sera gave negative passive transfer reactions. On the basis of these differences the authors distinguished sensitizing and immune antibodies as two distinct types. The latter type of antibody, directed against cow's milk antigen, was also found by them[5] in more than one-half of a group of normal nurslings kept on cow's milk. The presence of complement fixing antibodies to egg white in egg-white-sensitive eczematous children was confirmed by Stroble and Wasitzky.[6]

With a modified technique utilizing normal human hemolysins, Jaffe[7] demonstrated thermolabile complement fixing antibodies to extracts of fish, yeast, and linseed in the serum of asthmatic and eczematous patients whose cutaneous and passive transfer reactions were positive with the respective allergens. A similar technique was used by Albus[8-10] in studies on complement fixing antibodies in hay fever. He considered the complement fixation reaction to be a more useful guide in the diagnosis and treatment of hay fever patients than the cutaneous (scratch) test, in that the former was positive not only in most patients with a positive cutaneous reaction but also in clinically sensitive untreated individuals whose cutaneous tests gave negative results. He explained

*From the laboratories of the George Piness Allergy Group, Los Angeles, Calif.
†Author's address: 672 South Westlake Ave., Los Angeles 5, Calif.

this on the assumption that in the development of inhalant allergy the mucosa of the respiratory tract is the first tissue to become sensitized and that, subsequently, reagin appears in the blood stream and that the skin becomes sensitized only on further intensification of the sensitizing process. In established hypersensitivity he observed absence of sensitizing antibody in the serum during the winter months and reappearance in the hay fever season. He regularly observed a marked decrease in the titer of the complement fixing antibodies to pollen extract during the course of specific pollen desensitization and interpreted this as evidence of neutralization of reagin by the injected antigen. He claimed that the need for specific treatment could be determined by the serologic test—patients with negative or weak complement fixation reactions at the beginning of the hay fever season remained symptom-free without treatment. Hensel and Sheldon[11] also made complement fixation studies with the serum of hay fever patients by means of the technique employed by Jaffe and Albus. As antigens they used extracts of short ragweed, June grass, and orchard grass pollen. Although they obtained some degree of complement fixation in most untreated patients found sensitive by scratch test, no correlation was apparent between the serologic titers and the degree of the skin or the passive transfer reactions.

In our studies a modified technique of complement fixation was employed, following essentially the quantitative method described by Mayer, Osler, Bier, and Heidelberger[12] in which the maximum amount of complement fixed by an antigen-antibody mixture rather than the maximum dilution of serum or antigen fixing a given amount of complement is determined. Attempts with this method were thought to be worth while largely because promising preliminary results briefly reported elsewhere[13] were obtained in similar studies on autoantibodies to tissue antigens in rheumatic fever. For the present studies, the human complement contained in the test serum was utilized instead of guinea pig complement. Mixtures of active serum and antigen were incubated and the remaining complement activity was determined and compared with that of the same serum alone as well as with that of similar mixtures of control serum plus antigen and control serum alone.

MATERIALS AND METHODS

Patients' Serum.—Ten to 20 ml. of blood was obtained under sterile conditions and allowed to clot in the refrigerator for 18 to 48 hrs. The serum, separated by centrifugation, was stored frozen in 1 to 2 c.c. amounts in sterile tubes at –20° C. until use.

Hemolytic System.—Sheep red blood cells, collected in modified Alsever's solution[14] were used, each batch being satisfactory for 2 to 3 months. Before each use, a portion was washed with cold physiologic saline 4 to 6 times, made up to a 5 per cent suspension, and adjusted by cell count to contain 1 million cells per cubic millimeter.

Commercial rabbit antisheep hemolysin was titrated according to the method of Wadsworth.[15] For sensitization, equal amounts of cell suspension and a 1:2,000 dilution of the hemolysin (representing 4 hemolytic units) were mixed and incubated for 15 minutes at 37° C. immediately before use.

Antigens.—

Epidermal antigens: The raw material (hairs, feathers, dander), tightly packed in large percolators, was extracted continuously for 4 to 6 hours by recycling a solution containing 0.1 per cent sodium chloride, 0.3 per cent sodium bicarbonate, and some toluene. The pH was maintained at 8.0 to 8.5. The clear extract (about 6 liters), having been filtered by the passage through the percolator, was concentrated about 10 times in cellophane bags suspended in a current of air. The concentrate was filtered through paper if necessary and acidified to pH 4.7 with hydrochloride acid and immediately mixed with 3 volumes of acetone which had previously been cooled to minus 20° C. The resulting precipitate was collected on a Buchner filter, repeatedly washed with pure acetone, and dried. This dried material was stored in sealed bottles.

For use in complement fixation 1 Gm. of the dried epidermal antigen was extracted with 50 ml. of physiological saline containing 10 per cent normal human serum which had been inactivated for 30 minutes at 56° C. The serum was used because it was found that the anticomplementary properties of the antigen were greatly reduced thereby. After 1 to 2 hours at room temperature, the suspension was centrifuged and the clear supernate was stored frozen in 2 ml. samples until used. For skin tests, 2 Gm. of the same dried antigens were extracted with 100 ml. physiologic saline containing 1:25,000 phenylmercuric acetate and 50 per cent glycerol. This 1:50 extract sterilized by Seitz filtration was used for puncture testing, while a dilution of 1:1,000 (1:20 of the above extract) was employed for intradermal tests.

Pollen antigens: The dry pollen was extracted under continuous shaking for 1 hour with plain saline (without serum) in a proportion of 100 ml. per 3 Gm. of pollen. The clear filtrate was stored in frozen samples. For skin tests, 3 Gm. of pollen were extracted with 100 ml. of glycerosaline. The extract was used undiluted for puncture and diluted twenty fold for intradermal testing.

The saline used for the complement fixation tests contained 8.5 Gm. of sodium chloride and 100 mg. of magnesium chloride per liter.

Technique of Complement Fixation Tests.—The serum and antigen samples were thawed just before use. If necessary the antigen was filtered or centrifuged until clear. With regard to the optimal strength of the antigen, tests were made with a wide variation of antigen dilutions (up to several million). It was found, however, that the antigen had to be used in relatively low dilution. The concentrations finally adopted were as follows: dog hair and horse dander extract 1:100 (the original extract was diluted 1:2), goose feather extract 1:1000 (original extract diluted 1:20), and pollen extracts 1:33 (the original extract undiluted). In Kahn or Wassermann tubes immersed in ice water, 0.1 ml. portions of undiluted and unheated serum to be tested were mixed with 0.1 ml. of each antigen in the respective dilutions mentioned. In addition, a tube containing 0.1 ml. of serum only (no antigen) was set up for each serum sample. The pipetting was carried out as accurately as possible using 0.2 ml. pipettes. In all tubes, the volume was made up to 1.0 ml. with cold physiologic saline, and the contents were thoroughly mixed. The mixtures were left for fixation in the

refrigerator overnight. The following day, the residual complement activity of each mixture was titrated as follows: A series of 8 to 12 Kahn tubes immersed in ice water was set up for every mixture. Increasing amounts of the mixtures were then pipetted with greatest possible accuracy into these tubes, beginning usually with 0.01 ml. and ending with 0.3 ml. in each series (for instance 0.01, 0.015, 0.02, 0.03, 0.04, 0.05, 0.06, 0.08, 0.1, 0.15, 0.2, and 0.3 ml.). The same 0.2 ml. pipette was used throughout, being rinsed with saline before switching to a new mixture. In all tubes the volume was made up to 0.3 ml. Then 0.2 ml. of sensitized sheep cells was added, and the tubes were incubated for 15 minutes in a water bath at 37° C. If complete or nearly complete hemolysis in the tubes containing the largest amount of mixture was not reached after 15 minutes, incubation was prolonged for an additional 5 to 15 minutes. Immediately after incubation the tubes were chilled and then centrifuged for 3 minutes at about 1,400 r.p.m.

A color standard series was set up according to the method of Wadsworth,[15] using hemolysed and unhemolysed sheep cells, so that standards of 5, 10, 15, 20, 25 per cent, and so forth, up to 90 per cent hemolysis, were available. The percentage of partial hemolysis in each tube of the test series was then determined by visual comparison with the standard. It is believed that the experimental error resulting from visual inaccuracy was not more than ± 5 per cent. The values of partial hemolysis were plotted on graph paper against the amounts of human serum actually present in the respective tubes of each mixture of serum plus antigen or serum alone. The amount of serum of each mixture giving 50 per cent hemolysis was then determined from the curve of hemolysis. The 50%-hemolytic amount of each mixture of serum plus antigen was then compared with the control of the same serum alone:

$$R = \frac{\text{50\%-hemolytic amount of serum + antigen}}{\text{50\%-hemolytic amount of serum alone}}$$

If the ratio of the two values was approximately 1.0 (0.9 to 1.1), the reaction was negative. If the ratio was significantly greater than 1.0, complement had been fixed in the presence of the antigen, and the reaction was positive, provided that nonspecific anticomplementary effects were absent. However, since such anticomplementary effects were sometimes present to a slight or moderate degree, the ratio obtained for each mixture of test serum plus antigen to serum alone was compared with a similar ratio of a standard control serum plus the corresponding antigen to the standard control serum alone:

$$R' = \frac{\dfrac{\text{50\%-hemolytic amount of patient's serum + antigen}}{\text{50\%-hemolytic amount of patient's serum}}}{\dfrac{\text{50\%-hemolytic amount of control serum + antigen}}{\text{50\%-hemolytic amount of control serum}}}$$

The final values were expressed in terms of this ratio (R′). The reaction was considered positive when this ratio was 1.2 or greater in the case of the epidermal antigens, or 1.1 or greater in the case of the pollen antigens.

For the sake of illustration, a sample protocol shall be included:

SAMPLE PROTOCOL:

	PATIENT SERUM (ML.)	CONTROL SERUM (ML.)	EXTRACT OF DOG HAIR 1:100 (ML.)	POLLEN EXTRACT CYNODON DACTYLON 1:33 (ML.)	PHYSIOLOGIC SALINE (ML.)
Mixture A	0.1		0.1		0.8
Mixture B	0.1			0.1	0.8
Mixture C	0.1				0.9
Mixture D		0.1	0.1		0.8
Mixture E		0.1		0.1	0.8
Mixture F		0.1			0.9

Overnight incubation in the refrigerator.

Titration of residual complement activity:

TUBE NO.	1	2	3	4	5	6	7	8	9	10	11	12
Mixture A	0.01	0.015	0.02	0.03	0.04	0.05	0.06	0.08	0.1	0.15	0.2	0.3 ml.
Saline	0.29	0.285	0.28	0.27	0.26	0.25	0.24	0.22	0.2	0.15	0.1	— ml.
Sensitized sheep cells	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2 ml.

A similar series was set up for each of the other mixtures (B, C, D, E, F). The amount of complement bearing human serum present in each tube was, of course, one-tenth of the amount of mixture. All tubes were incubated in a water bath at 37° C. After centrifugation, comparison with the color standards showed the following percentages of hemolysis in the respective tubes:

TUBE NO.	1	2	3	4	5	6	7	8	9	10	11	12
Amount of serum present	0.001	0.0015	0.002	0.003	0.004	0.005	0.006	0.008	0.01	0.015	0.02	0.03
Hemolysis:												
Mixture A									20	35	57.5	80
Mixture B			22.5	42.5	67.5	80	90					
Mixture C	22.5	30	40	60	77.5	90						
Mixture D	20	25	35	60	80	95						
Mixture E	15	20	40	70	90							
Mixture F	10	25	42.5	75	95							

From plotting of these values of hemolysis and constructing the hemolytic curve the following amounts were found to represent the 50%-hemolytic doses:

Mixture A (patient serum + dog hair)	0.0183 ml.
Mixture B (patient serum + *Cynodon dactylon*)	0.00325 ml.
Mixture C (patient serum)	0.0025 ml.
Mixture D (control serum + dog hair)	0.0026 ml.
Mixture E (control serum + *Cynodon dactylon*)	0.0023 ml.
Mixture F (control serum)	0.0022 ml.

The ratios as defined above are then:

$$R_A = \frac{A}{C} = \frac{0.0183}{0.0025} = 7.32$$

$$R_B = \frac{B}{C} = \frac{0.00325}{0.0025} = 1.3$$

$$R_D = \frac{D}{F} = \frac{0.0026}{0.0022} = 1.18$$

$$R_E = \frac{E}{F} = \frac{0.0023}{0.0022} = 1.03$$

$$R'_A = \frac{R_A}{R_D} = 6.2$$

$$R'_B = \frac{R_B}{R_E} = 1.25$$

RESULTS

One or several serum samples from 23 allergic children and from 12 adults before institution of specific treatment were studied. Repeated samples from 7 allergic adults who were under continuous specific treatment and from whom no pretreatment sera were obtainable were also tested and, as controls, standard serum samples from 5 clinically nonallergic adults were employed, in which the complement fixation test was negative. Most serum samples were tested repeatedly with the same set of antigens of the same or a different batch. On the whole the reactions proved to be reproducible, although not in a strictly quantitative sense. Strong or moderately strong reactions could be elicited consistently in repeated tests. Weak or doubtful reactions, however, were not always reproducible. The results are summarized in Tables I and II. As seen from these, the reactions with the epidermal antigens were considerably stronger and occurred with greater frequency than those with the pollen antigens. A comparison with the results of skin tests shows that a high percentage of those patients giving positive skin reactions to epidermal antigens also had complement fixing antibodies to these antigens in the serum. No constant parallelism is apparent, however, between the intensity of the skin reactions and the titer of complement fixing antibodies. Further, there were some patients with negative skin reactions and positive complement fixation, although usually slight. There were also patients with positive skin reactions and negative complement fixation. Neither of these discrepancies is surprising in the light of what is generally known or assumed on the dynamics of immunization and sensitization—circulating antibodies may be present without the skin having become sensitized and, conversely, sensitization of the skin may exist while circulating antibodies have disappeared or may never have been present. The additional factor making for discrepancies is that skin tests were not done at the same time as the blood for serologic studies was obtained, the difference in time having been often weeks or even months. The passive transfer reactions recorded were done, however, with the same sera used for the serologic tests. The correlation between positive passive transfer reactions and positive complement fixation was better, at least in the case of the epidermal antigens, than the correlation of the latter with the direct skin tests; here also, a few discrepancies may be noted. It is noteworthy that the correlation between the direct skin test and the passive transfer reaction also fails to be complete. The fact that the complement fixation with pollen antigens yielded somewhat poorer results with regard to correlation with the other tests and that, generally, the reactions were much weaker, may be due to lesser potency of these antigen preparations (a lower content of active substance in the extracts used), or to other factors.

The effect of specific treatment on the titer of complement fixing antibodies to the same antigen used in treatment was investigated in 21 patients. The specific treatment consisted of weekly subcutaneous injections, beginning usually with 0.05 ml. of a 1:50,000 dilution of the mixture of the epidermal antigens or with 0.05 ml. of a 1:5,000 dilution of the pollen extract mixture. The increase in dosage was such that, on the average, after each fifth injection, a 10 times

TABLE I. ALLERGIC CHILDREN BEFORE SPECIFIC TREATMENT

PATIENT	CLINICAL DIAGNOSIS	ANTIGEN																	
		DOG HAIR			HORSE DANDER			GOOSE FEATHERS			AMBROSIA ELATION			CYNODON DACTYLON			LOLIUM PERENNE		
		CF	ST	PK	CF	ST	PK	CF	ST	PK	CF	ST	PK	CF	ST	PK	CF	ST	PK
1. SA	E	–	P4	4	1.3	P4	3	11.3	P4	4++	–	P2	4	–	P2	4	–	P2	4+
2. WR	R, A	6.2	I4	2	2.0	–	2	> 7.2	I3	4+	3.5	I2	3	1.24	I4	4	–	P3	4+
3. BR	R, A	1.4	I3	2	1.3	I3	3	2.5	I4	4	1.3	I2	4	1.2	I4+	3	1.2	I4	4+
4. SE	R, A	–	I2	–	–	I2	3	–	P4+	4+	–	–	–	–	P2	3	1.14	P4+	4+
5. BRI	R, E	2.8	P4	3	2.8	I2	3	>13.0	P4	4++	1.7	P2	–	1.4	I3	–	1.2	I2	–
6. WO	R, A	1.3	I2	2	1.3	I2	2	3.6	I3	4+	–	–	3	1.16	–	4	1.2	P3	4+
7. FI	R, A, C	1.5	I2	–	1.2	I2	–	1.8	P4	2	–	–	–	1.17	–	–	1.2	–	–
8. GO	HF, A	1.7	P2	2	1.25	I2	2	1.4	I4	4	1.13	I2	–	1.4	–	2	–	–	–
9. FE	C	1.8	I4	–	1.6	I2	–	–	I2	2	1.29	–	–	1.12	–	–	1.25	–	–
10. FR	R, A	1.3	P4	3	1.26	–	2	8.6	P4++	4+	–	–	–	1.2	I4	–	1.3	P2	–
11. BE	R, A	1.5	I3	2	1.3	–	–	7.3	P4	3	–	–	–	–	I2	3	–	I2	2
12. BA	R, A	2.2	I4+	4+	1.7	I4+	4+	13.0	P2	4++	1.24	I4+	4+	1.1	I3	4	1.16	I4	2
13. GA	R, A	–	I4	–	–	I2	–	7.2	I4		1.5	–		1.2	I3		1.3	I3	
14. CO	A	2.2	I3		1.5	I2		4.4	I4		–	–		–	I2		1.15	I3	
15. EL	R, A	1.8	I2		1.5	I2		4.3	I3		1.24	I2		1.23	I3		1.1	I3	
16. ME	R, A	2.3	P2		1.9	P4+		>15.0	P4++		1.34	–		1.33	P2		1.21	P4+	
17. YO	R, U	–	I2		–	–		2.0	I3		–	–		–	I2		–	–	
18. PA	R, A, E	1.8	I4		–	I3		10.0	P4		–	–		–	P3		–	P4	
19. IO	R, A	–	I3		–	–		–	I3		–	–		–	–		–	I2	
20. BI	A	1.8	I3		1.36	–		>8.0	–		1.5	–		1.2	–		1.14	–	
21. SH	R, A	1.8	I2		1.7	I2		8.0	I2		–	–		–	–		–	–	
22. SCH	R, A	1.3	P2		–	I3		1.8	P4+		1.3	I2		1.3	I2		1.28	–	
23. RO	R	1.25	I3		1.3	I2		>10.0	P2		–	–		–	–		–	–	
Per cent positive		78	100	75	74	74	75	87	96	100	48	35	42	61	65	67	61	65	58
Per cent of ST-positive patients giving positive CF			78			77			87			88			60			67	
Per cent of PK-positive patients giving positive CF			89			89			83			60			63			57	
Per cent correlation between CF and ST (both either pos. or neg.)			78			65			83			78			52			61	
Per cent correlation between CF and PK			75			67			83			58			42			42	
Per cent correlation between ST and PK			75			58			100			75			75			83	

Legend: E = eczema
R = allergic rhinitis
A = asthma
C = conjunctivitis
U = urticaria
HF = seasonal hay fever

CF = complement fixation (expressed as quotient $\frac{\text{C'50 test S + A}}{\text{C'50 test S}} / \frac{\text{C'50 stand. S + A}}{\text{C'50 standard S}}$
ST = skin test (graded 2 to 4+), P = puncture test, I = intradermal test
PK = Prausnitz-Küstner reaction (passive transfer), graded 2 to 4+
– equals reaction negative

HF = seasonal hay fever

TABLE II. ALLERGIC ADULTS

(Patients 24 to 36 Before Specific Treatment; No Pretreatment Sera Available From Patients 37 to 42)

PATIENT	CLINICAL DIAGNOSIS	ANTIGEN																	
		DOG HAIR			HORSE DANDER			GOOSE FEATHERS			AMBROSIA ELATION			CYNODON DACTYLON			LOLIUM PERENNE		
		CF	ST	PK	CF	ST	PK	CF	ST	ST	CF	ST	PK	CF	ST	PK	CF	PK	PK
24. CA	A	3.4	I3	–	6.2	I2	2	12.0	I4	4	1.7	I2	–	1.13	I2	2	–	–	–
25. FEL	R, A	1.4	–	–	1.3	–	–	12.0	I4	–	1.26	–	–	–	–	–	–	–	–
26. WA	HF, U	7.7	P2	2	3.7	I2	–	>14.0		I2	2.2	P2	–	1.2	I2	–	–	I2	–
27. SP	A	–	–		–	–		–	I3		–	–		–	–		1.25	–	–
28. HO	R, A	–	I3		1.9	I3		–	I4		–	I4		–	I2		–	I2	
29. SHO	A	1.9	I3		1.7	I4		10.0	P3		–	I3		1.2	P2		1.2	P3	
30. LE	R	3.8	I3		8.9	P2		9.3	–		1.3	–		1.1	–		–	–	
31. ER	A	3.4	I2		1.4	–		–	I3		–	P4		–	P3		–	P3	
32. NI	A	3.1	I3		1.6	I2		>9.0	P4		–	I2		–	I2		–	I2	
33. FO	R, U	1.5	–		1.28	–		>10.0	P2		–	–		–	–		–	–	
34. GOL	R	1.3	I4		1.3	I3		7.6	P2		–	I3		1.1	P4		1.14	P4	
35. DA	R, C	–	I2		1.26	–		7.2	–		–	–		–	–		–	I2	
36. RE	A	–	I3	2	3.0	P4	3	–	P4	2	1.4	P4	4+	–	P3	2	–	I2	–
37. JU	A	–	I4		1.35	I2		3.7	I3		1.1	I3		–	I2		–	I3	
38. TR	R, A	1.23	I4	2	4.2	I3	–	10.2	P2	3	4.1	P4	–	–	P3	–	–	–	–
39. RA	HF, A, U	1.4	P3	2	1.21	P2	2	4.0	P3	–	1.6	I3	2	–	I4	4+	–	–	–
40. GOS	R, E	1.27	–	2							1.6	I4	4+						
41. BALT	R, A, C	1.3	I2	2	1.7	I2	–	9.5	P4	4++	–	–	–	–	I2	–	–	I2	–
42. TH	R, A	1.2	P4+		–	I3		2.5	I2		–	P4		–	–				
Per cent positive		74	79	75	89	72	43	78	89	71	47	68	38	28	67	43	18	59	0
Per cent of ST-positive patients giving positive CF				73		92			75			54			33			20	
Per cent of PK-positive patients giving positive CF				83		100			80			100			33				
Per cent correlation between CF and ST (both either positive or Neg.)				58		72			67			58			50			47	
Per cent correlation between CF and PK				63		43			57			38			57			100	
Per cent correlation between ST and PK				75		57			71			62			57			57	

For legend to table, see Table I.

stronger antigen dilution was begun. Blood samples for serologic tests were obtained immediately before an injection (1 week after the last injection), when the patients had been through 6 to 16 weeks of treatment. In each complement fixation test of post-treatment serum, pretreatment serum from the same patient was also tested to obtain comparable results. Table III summarizes the findings. It may be seen that in almost one-half of the cases no definite change in the serologic reaction occurred after treatment as compared to before treatment with any given antigen. In the larger portion of the remaining cases, a decrease in the reaction or a complete disappearance was observed, while a small portion exhibited an increase in antibody titer. The latter was usually slight when it occurred, in contrast to the cases showing a decrease where a marked drop in titer was not uncommon. Some doubt is thrown on the significance of these changes by the fact that a parallel change in reactivity of the same post-treatment sera with antigens other than the ones injected was not infrequently also observed. Whether or not this might be due to immunologic relationships between the various antigens tested and used for treatment cannot be decided with present knowledge regarding specificity. However, the results do seem to indicate that, if the complement fixing antibodies to allergens are at all specifically affected by desensitizing injections, they tend to decrease in titer or disappear altogether rather than to augment. This is in line with reports of previous workers[3, 8, 10] and with the old belief that the beneficial effects of specific treatment are, at least in part, due to binding of reagin by the allergen injected in small doses.

Because of the findings of Cooke and his co-workers[16] and Loveless,[17] and confirmed by numerous others, of formation of blocking antibodies in response to treatment with low ragweed extract and the reported thermostability of these antibodies, the effect of heating pre- and post-treatment sera for 4 hours at 57° C. was investigated. For complement, 0.1 ml. of normal active serum was added to each tube containing 0.1 ml. of inactivated test serum and antigen. Some of the results are given in Table IV. As shown in this table the heated sera reacted considerably less than the same sera unheated. However, positive reactions although considerably diminished, were not abolished by the inactivation process, this being true of the pre- as well as the post-treatment sera. There was, further, no evidence from this experiment that the post-treatment sera contained a larger proportion of heat-stable antibodies than the pretreatment sera. The change in titer occurring after specific treatment was in the same direction whether the sera were heated or not. Therefore, there is no indication that the complement fixation reaction is able to distinguish sensitizing from blocking antibodies, provided that the latter existed in our sera. In this connection it may be noted that the extent of specific treatment was less in this study than in most of those dealing with blocking antibodies and further, none of the patients had been treated with low ragweed extract, the allergen used predominantly for the latter studies.

Collodion Particle Technique.—A number of attempts were made to demonstrate antibodies to the same epidermal and pollen antigens by means of the collodion particle technique in the modifications used in previous studies.[18]

TABLE III. SEROLOGIC RESULTS BEFORE AND AFTER SPECIFIC TREATMENT

PATIENT	LENGTH OF TREATMENT OF 1 WEEKLY INJECTION (WKS.)	ANTIGEN (FOR SEROLOGIC TESTING AND TREATMENT)									
		DOG HAIR		HORSE DANDER		GOOSE FEATHERS		CYNODON DACTYLON		LOLIUM PERENNE	
		A	P	A	P	A	P	A	P	A	P
2. WR	16							1.24	1.17	–	1.15
3. BR	6							1.22	–	1.21	–
4. SE	16	–	–			–	–				
5. BRI	10	2.8	–			>4.5	>4.5				
6. WO	10	1.2	1.3	1.2	1.3	1.5	1.8				
7. FI	9	1.5	1.28			1.8	–				
8. GO	12	1.4	1.4			–	2.6				
10. FR	8	1.3	–			8.6	>8.7	1.2	–		
12. BA	8	1.6	–	1.3	–	>8.0	–	–	1.14		
13. GA	13	–	–			7.2	>13.0				
14. CO	13	2.2	3.3	1.5	1.5	4.4	>4.0				
15. EL	6	1.9	1.7	1.5	1.39	3.8	3.5				
16. ME	14	2.3	–	1.9	–	>15.0	1.4	1.13	–	1.12	–
18. PA	13	>10.0	8.0			>10.0	>8.0				
20. BI	13	1.8	1.2			>15.0	10.3				
21. SH	9	1.8	1.9			6.2	3.1				
22. SCH	9	1.3	–			1.8	–				
23. RO	9	–	1.2			10.0	>10.0				
24. CA	13	10.0	10.0	6.2	4.2	15.0	15.0	1.1	1.1	–	1.2
29. SHO	10							1.2	1.14	1.2	1.2
30. LE	10			8.9	11.5	9.3	>16.0				
Effect of specific treatment on titer:											
Increase		2 (12%)		1 (14%)		4 (22%)		1 (14%)		2 (40%)	
Decrease		7 (41%)		3 (43%)		6 (33%)		3 (43%)		2 (40%)	
No change		8 (47%)		3 (43%)		8 (45%)		3 (43%)		1 (20%)	

Various techniques of sensitization of the collodion particles and various procedures as to incubation and other factors were tried. Sera reacting very strongly by complement fixation as well as moderately and nonreacting ones were employed. The results were negative. There seems little doubt, therefore, that the antibodies in question have no precipitating properties.

TABLE IV. EFFECT OF INACTIVATION OF SERA FOR FOUR HOURS AT 57° C.

SERUM	ANTIGEN					
	DOG HAIR	HORSE DANDER	GOOSE FEATHERS	AMBROSIA ELATION	CYNODON DACTYLON	LOLIUM PERENNE
Unheated: BA, pretreatment	1.1	1.3	>8.0	1.24	1.1	1.16
BA, post-treatment	1.6	1.1	3.1		1.14	
Heated: BA, pretreatment	1.25	1.18	2.26	1.16	1.13	1.08
BA, post-treatment	1.1	1.18	1.38		1.14	
Unheated: WR, pretreatment	6.2	2.0	>7.2	3.5	1.24	
WR, post-treatment					1.17	1.15
Heated: WR, pretreatment	1.33	1.37	2.62	1.23	1.17	1.2
WR, post-treatment					1.02	1.04
Unheated: LE, pretreatment	3.8	8.9	9.3	1.3	1.1	
LE, post-treatment		11.5	>16.2			
Heated: LE, pretreatment	1.27	1.78	>7.0	1.3	1.16	1.1
LE, post-treatment		2.1	>7.0			

COMMENT

From the results described it is evident that the majority of allergic individuals have antibodies in their serum which fix complement in the presence of extracts of epidermal antigens. Complement fixing antibodies for some common pollen antigens were also observed, but in a lower incidence. These findings are in agreement with the higher incidence of positive whealing reactions to epidermal antigens as compared to the pollen reactions. When the results of the complement fixation tests are compared with the skin reaction in each individual patient, no consistent parallelism is observed between the titer of the complement fixing antibodies and the intensity of the skin reaction. However, when the results are compared on the basis of either a positive or a negative reaction, a fair correlation appears to prevail, especially with respect to the epidermal antigens, in that, of the patients giving a positive skin reaction with the various antigens, from 77 to 92 per cent also showed a positive serologic reaction. It should be pointed out that the correlation between the direct skin and the passive transfer reaction was approximately of the same order (or only slightly better). The patients were in no way selected but represented a group of consecutive admissions to the clinics. Since the specific treatment instituted is based on clinical appraisal including history as well as on the skin reactions, the antigens prescribed for hyposensitization may be considered to represent roughly the most important factors in the patients' inhalant allergy. In these clinics, the proportion of the number of patients treated with epidermal antigens to that treated with pollen antigens is of the order 2:1. The extent and incidence of the complement fixing antibodies would bear this out.

The question arises whether the complement fixing antibodies are identical with reagin (skin-sensitizing antibodies). This question cannot be definitely answered on the basis of these studies. The fact of the high incidence of complement fixing antibodies in the sera of allergic individuals together with the fact that antibodies are not demonstrable with other serologic methods—especially such a highly sensitive method for the detection of precipitins as the collodion particle technique—seems to point in the direction of the possible identity of the complement fixing with the reaginic antibodies, or at least of a relationship between the two. The results indicating that the greater part of the complement fixing antibodies are thermolabile, as are the skin-sensitizing antibodies, also is a point in favor of this possibility. On the other hand, there are enough discrepancies between the direct skin reaction or the passive transfer reaction and the serologic results in certain patients to make any conclusions doubtful. Also, one would expect that in addition to any sensitizing antibodies which may be demonstrable, other antibodies present, such as natural antibodies or antibodies resulting from immunization, would also react in the complement fixation tests.

One aspect of the problem has not been investigated in this study, namely, the incidence and extent of complement fixing antibodies to these allergens in nonallergic control subjects. Since it is to be expected that the presence of such antibodies, if at all, would correlate with the skin-sensitizing antibodies, and

thus to some extent with the skin tests, rather than with clinical symptoms, it would be necessary to study clinically nonallergic control subjects in which the corresponding skin reactions are known. Such individuals were not available for these investigations, with the exception of two persons whose blood, which was obtained for control purposes, showed positive complement fixation results. A subsequent inquiry and skin tests revealed that both had positive skin reactions and one of them mild clinical symptoms. Because of the probability of sensitization of a large number of individuals without definite symptoms of clinical allergy, a considerable incidence of positive complement fixation, especially with the use of epidermal antigens, might be expected in unselected control subjects.

It is clear that the serologic technique used in these studies would not be suitable for routine diagnostic or prognostic purposes in allergic patients, for there is no evidence so far that it would yield more reliable results than the skin test, and, especially, the technique would be far too difficult and laborious for general use. But the complement fixation reaction, either in the general procedure employed here or possibly the one used by Jaffe,[7] Albus,[8-10] and Hensel and Sheldon,[11] might well prove of considerable value in studies of the mechanism of sensitization, desensitization, and immunization. This belief is strengthened by the fact that very strong reactions may be observed while the highly sensitive collodion particle technique fails to give any results. There would be room for technical improvement, of course. Photoelectric determination of the degree of hemolysis would probably increase the accuracy of the tests somewhat. Evaluation of the optimal dose of antigen for each individual serum and possibly the use of larger doses of serum might improve its sensitivity. However, the most important factor would be improvement of the test antigens, both epidermal and pollen. In our experience these antigens gradually deteriorated over a period of weeks to months, even when stored in the frozen state, so that the specific reactions became weaker while the anticomplementary properties increased greatly. Minor changes on storage may also take place in the serum. Preservation at carbon dioxide ice temperature might be preferable. The variation in the strength of the reactions observed in our studies can at least in part be explained on deterioration. It would also be desirable to employ the same standard nonreactive serum for all tests, provided that a large amount is available and that it can be preserved without change. In that case, standardization of antigens with pools of standard reaginic serum might also be a possibility.

SUMMARY

Complement fixation tests were carried out on the sera of 42 patients with various types of clinical allergy, using epidermal and pollen antigens. It was found that a high proportion of the cases sensitive by skin test had complement fixing antibodies to epidermal antigens. The same was observed for pollen-sensitive individuals, but in a lower incidence. The possible significance of these findings has been discussed.

REFERENCES

1. Swineford, O., Jr., and Houlihan, R.: Antibodies to Ragweed Extract, J. ALLERGY **18**: 190, 1947.
2. Cavelti, P. A.: Unpublished observation.
3. Walker, I. C.: Complement Fixation and Precipitin Reactions With the Serum of Bronchial Asthmatics Who Are Sensitive to the Proteins of Wheat, Horse Dandruff, Cat Hair and Bacteria, Using These Proteins as Antigens in the Cutaneous Reactions as an Index of Sensitization, J. Med. Research **36**: 243, 1917.
4. Gyoergy, P., Moro, E., and Witebsky, E.: Eiklarempfindlichkeit bei Eczema infantum, Klin. Wchnschr. **9**: 1012, 1930.
5. Gyoergy, P., Moro, E., and Witebsky, E.: Milchantikoerper im Serum von Saeuglingen, Klin. Wchnschr. **10**: 821, 1931.
6. Stroble, A., and Wasitzky, A.: Untersuchungen ueber die alimentaere Allergie des Ekzemkindes mit besonderer Beruecksichtigung der Eiklarempfindlichkeit, Monatschr. f. Kinderh. **54**: 53, 1932.
7. Jaffe, K.: Nachweis spezifischer Antikoerper in vitro bei hochgradiger Fisch und Hefeallergie, Klin. Wchnschr. **10**: 304, 1931.
8. Albus, G.: Beeinflussung der Antikoerpenkonzentration durch spezifische Desensibilisierung bei Pollenallergie, Ztschr. f. d. ges. exper. Med. **95**: 703, 1935.
9. Albus, G.: Serologische Allergenbestimmung bei Pollenkrankheit unter Beruecksichtigung des Antikoerpertiters, Ztschr. f. d. ges. exper. Med. **96**: 710, 1935.
10. Albus, G.: Uber die Wirksamkeit von Mischextrakten bei Behandlung der Pollenallergie, Ztschr. f. d. ges. exper. Med. **97**: 756, 1936.
11. Hensel, M. E., and Sheldon, J. M.: Complement Fixation With Specific Allergens in Hay Fever, J. Lab. & Clin. Med. **26**: 1586, 1941.
12. Mayer, M. M., Osler, H. J., Bier, O. G., and Heidelberger, M.: Quantitative Studies on Complement Fixation I. A. Method, J. Immunol. **59**: 195, 1948.
13. Cavelti, P. A.: Sensitization With Tissue Antigens, 7th Internat. Congr. Rheumat. Dis., New York, 1949, W. B. Saunders Company.
14. Bukantz, S. C., Rein, C. R., and Kent, J. F.: Studies in Complement Fixation; Preservation of Sheep's Blood in Citrate Dextrose Mixtures (Modified Alsever's Solution) for Use in Complement Fixation Reaction, J. Lab. & Clin. Med. **31**: 394, 1946.
15. Wadsworth, A. B.: Standard Methods, Baltimore, 1939, Williams & Wilkins Company.
16. Cooke, R. A., Barnard, J. H., Hebald, S., and Stull, A.: Serological Evidence of Immunity With Co-existing Sensitization in a Type of Human Allergy (Hay Fever) J. Exper. Med. **62**: 733, 1935.
17. Loveless, M. H.: Immunological Studies of Pollinosis. I. The Presence of Two Antibodies Related to the Same Pollen Antigen in the Serum of Treated Hay Fever Patients, J. Immunol. **38**: 25, 1940.
18. Cavelti, P. A.: The Technic of Collodion Particle Agglutination., J. Immunol. **57**: 141, 1947.

CASTOR BEAN: AN INDUSTRIAL HAZARD AS A CONTAMINANT OF GREEN COFFEE DUST AND USED BURLAP BAGS

KARL D. FIGLEY, M.D., AND FRANK F. A. RAWLING, M.D., TOLEDO, OHIO

SINCE April, 1949, we have discovered 9 cases of sensitivity to the castor bean allergen. All 9 patients suffered severe symptoms of acute allergic rhinitis and/or asthma from inhaling the allergen. The patients were all adults. Four of them worked in the office of 1 coffee-roasting plant in Toledo; a fifth was employed to seal cartons containing sacks of roasted coffee in the same plant. Two other patients had worked in the warehouse of another coffee roasting plant in Toledo, thus making altogether 7 patients connected with the coffee-processing industry. Patients 8 and 9 worked in factories devoted to stamping small metal parts, in no way connected with the coffee industry. All 9 of these patients gave strongly positive skin reactions by scratch test to castor bean allergen. All 9 owed their difficulty to breathing dust from burlap bags which had at one time contained, or had been contaminated by, castor beans or castor bean pomace.

The 4 office workers were in a large open office occupied by some 60 people. This office was separated from the coffee-storage warehouse by only a corridor containing several open ventilating windows near the ceiling. A swinging door gave access to the warehouse from the corridor. A men's washroom opening off the office at the side opposite the corridor contained a large exhaust fan, operated during working hours. Thus this fan pulled a large volume of air from the coffee warehouse, through the swinging door and then into the office, through the open ventilating windows lining the corridor.

The storage warehouse held 1 or more freight trainloads of bags of green coffee. Near the office side of the warehouse were 2 cleaning machines. Into the hopper of these machines several bags of green coffee were poured at a time. By a shaking process the hull and chaff were removed from the beans. The area for some distance around the machines was inches deep with this green coffee dust, and of course the ventilating fan, above-mentioned, pulled much of this dust into the office through the open windows of the corridor. Dust was plainly visible on many of the office desks. We shall refer to this dust as "green coffee dust" to denote that it originated from the cleaning process applied to raw (green) coffee beans.

Patient 5, a young man of 27 years, had worked at this same coffee-roasting plant for 16 months. His job was to seal cartons of 1-pound sacks of roasted coffee as they came from the weighing machine. Ordinarily, he had no trouble doing this work. On several occasions during rush periods, he had been obliged to help unload bags of green coffee from freight cars. Recently, each time at this job, he had developed severe attacks of asthma incapacitating him for several days. He identified the green coffee dust as the cause of his asthma, for he had an immediate attack when collecting some of this dust.

Patients 6 and 7, 2 coffee warehouse employees, handled bags of green coffee in a roasting plant located several miles from the 1 first mentioned. Conditions were exactly similar there so far as exposure to green coffee dust was concerned; the same shaking process was used to clean the raw coffee beans. After some years of employment both these men were obliged to quit

their jobs; one in 1939, and one in 1944, because of frequent severe asthma which they attributed to the green coffee dust.

Patient 8 had run a pressing machine for 8 years in a factory that stamps out small metal parts. In early fall of 1949 he noted much sneezing, particularly at work. On October 28, he developed his first severe, acute asthma, lasting 3 days. This patient made the observation that his sneezing was often associated with shaking out a burlap bag that was used to hold small metal parts as they came from the machine. These bags came from a pile of second-hand burlap bags. Not every bag would cause sneezing.

Patient 9,* a man of 30 years, was a shipping clerk for a Columbus manufacturing and supply company. In October, 1941, he began to have frequent attacks of asthma, for which he first consulted Dr. Mitchell in January, 1942. At that time he gave minor positive skin tests to flaxseed and kapok seed. Foods, pollens, mold spores, and other inhalants, including house dust, gave negative tests.

Dr. Mitchell's further history was as follows: "On February 19, 1942, he reported severe asthma while handling burlap sacks used to ship castings and mentioned the sacks had been used before because there were beans in some of them. He recalled that on February 6, 20 minutes after entering the plant, his eyes became red, swollen, and itchy. He could not see and had to be led away from the room where he was working. His forehead and neck were covered with hives, but he had no asthma on this occasion.

"A test with my own burlap extract was negative. He was asked to bring in some of the sacks from the plant. A few beans were found in the seams, and these were sent to Dr. Karl Figley for identification, since it was suspected they were castor beans. The sacks were labeled in Spanish or Portuguese. Dr. Figley identified the beans as castor beans, by extracting them and testing a known castor bean-sensitive patient with the extract. Puncture test with an extract from the beans as well as an extract made from the burlap sack were strongly positive on the patient."

The two coffee-roasting plants, referred to previously, imported coffee from Brazil and Colombia, South America. For the most part the coffee was shipped in new bags, either so-called "grass bags" (caroa fibre) or burlap (jute) bags. However, we were informed that during World War II, when new bags were not procurable, coffee was occasionally shipped in used bags. (We suspect that this practice still obtains at times.)

Castor bean is the seed of the plant, *Ricinus communis*. This plant is extensively grown in South America. Castor bean is shipped in burlap bags to various ports chiefly on the eastern United States coast. From there the bags of castor beans are transshipped by freight to crushing mills located principally on the East Coast. There the oil is pressed from the beans. The "cake" or residue remaining is ground into powdered form. This is known in the trade as castor pomace. Its chief use is for fertilizer.

From the above it is apparent that bags of green coffee may become contaminated by castor bean allergen in several ways: (1) green coffee may be

*The history of Patient 9 is included through the kindness of Dr. John H. Mitchell of Columbus, Ohio.

shipped from South America in used bags that previously contained castor beans or castor pomace; (2) bags of green coffee may become contaminated in the holds of vessels, that contain or, more likely, previously contained bags of castor beans; and (3) bags of green coffee may become contaminated in freight cars which previously contained bags of castor beans or castor pumace.

We mention these possibilities because executives in the coffee-roasting plants insist that the green coffee they import is shipped only in new, unused bags. Unfortunately, we have been unable to secure from the coffee warehouses a bag that has been unquestionably contaminated with castor bean or castor pomace. One has no way of selecting such a bag from the thousands of bags in storage.

When first asked to ascertain the cause of the severe symptoms in the 4 office workers, we assumed, after surveying the premises, that it was the green coffee dust. Upon further testing when all gave more strongly positive skin reactions to castor bean allergen, we knew this was more than a coincidence. However, from this study it is interesting to note that in several cases the coffee fraction in the green coffee dust was a factor as well as the castor bean component of the dust. Later, we will discuss this observation more fully.

TABLE I. REACTIONS TO SCRATCH TESTS

CASES	GREEN COFFEE DUST (CONTAINS CASTOR BEAN COMPONENT)	WASHED EXTRACT OF COFFEE BEAN (NO CASTOR BEAN COMPONENT)	CASTOR BEAN ALLERGEN CB-1A	OTHER REACTIONS (30 ROUTINE TESTS)
1. Office worker	++	Negative	++++	None
2. Office worker	+++	++	++++	Flaxseed +
3. Office worker	+++	+++	++++	House dust +
4. Office worker	++	++	+++	Flaxseed +
5. Coffee sealer	++	Negative	++++	None
6. Warehouse workers	++	Negative	++++	None
7. Warehouse worker	+++	+++	++++	House dust ++++ Ragweed +++
8. Press operator	++	Negative	++++	Cottonseed + Flaxseed +
9. Shipping clerk (Dr. Mitchell's case)	Not done	Not done	++++	Kapok seed + Flaxseed ++
10. Manager of coffee-roasting plant	+++	+++	Negative	House dust +
50 control cases of allergic rhinitis and asthma	Negative	Negative	Negative	

Table I shows that the first 9 patients listed all reacted strongly by scratch (dermal) test to purified castor bean allergen.[1] Eight of these also reacted to green coffee dust extract, which represented a mixture of coffee bean allergen plus a minute component of castor bean allergen. (Case 9, Dr. Mitchell's patient, was not tested with coffee dust or coffee bean extract.) Four of the 8 failed to react to an extract of green coffee beans carefully washed to exclude castor bean contaminant. Thus it may be assumed that 4 of the 8 patients are sensitive to castor bean allergen only, while the other 4 are sensitive, not only to castor bean allergen, but to a lesser degree to the coffee bean allergen present in the green coffee dust.

A tenth case is listed in Table I. This was the manager of 1 of the coffee-roasting plants who has held this position for 20 years. He was first seen in 1941 with the complaint of perennial rhinitis and occasional asthma which he attributed to inhalation of green coffee dust. Tests done at that time gave positive skin reactions to this dust. When the present study was begun in 1949, he again reacted to an extract of green coffee dust and 1 of washed coffee bean, but failed to react to castor bean allergen.

We said above that for various reasons we have been unable to secure from a coffee-roasting plant or the metal-stamping plant a burlap bag that unquestionably had contained castor bean or castor pomace. For proof of our thesis, it is necessary to demonstrate the presence of castor bean allergen in such a bag. However, we do have a supply of green coffee dust collected from the vicinity of the cleaning machines in one of the coffee-roasting plants. This dust answers the same purpose as a bag would, for the dust came only from green coffee shipped in burlap or "grass" bags. This green coffee dust is a fine, tan-colored powder mixed with particles of hull and chaff from the raw coffee. It contains some twigs and other extraneous matter, and in particular, contains innumerable tiny fibers of the burlap bags. (None of our patients reacted on skin test to an extract made from a new burlap bag.)

We have assumed that green coffee dust consists not only of the chaff of the coffee bean principally, but that it contains a more or less minute component of castor bean allergen from bags that have been contaminated by contact with castor bean or castor bean pomace. We know that the CB-1A fraction of castor bean is heat stable.[1] We assumed that the coffee bean allergen was heat labile. Therefore, it occurred to us that boiling green coffee dust extract would inactivate its coffee allergen, but leave unaltered the castor bean allergen present. By testing a patient who reacted to both castor bean and coffee bean, with boiled extracts of green coffee dust and raw coffee bean, if he reacted to the test with boiled green coffee dust but failed to react to boiled extract of washed coffee bean, this would speak for the presence of the heat-stable castor bean allergen in the green coffee dust.

Patient 7 was available for study. He was a man of 48 years who was obliged to quit his job at the roasting plant in 1939 because of severe asthma. Following this he remained asthma-free for some time, but consulted us recently because of recurrence of asthma in mild degree. This was found to be due to sensitivity to house dust and ragweed pollen.

From Table II, it is seen that our patient initially reacted to green coffee dust, green coffee bean, and castor bean, as well as to house dust and ragweed pollen. However, our experiment struck a snag, for we found that boiling for 6 minutes, and even autoclaving for 20 minutes at 15 pounds' pressure (250° C.) failed to inactivate the coffee bean extract. Therefore, it appears that coffee bean contains an important allergenic fraction that is heat stable. This has not been stressed in the literature. It has been our impression that the rare cases of coffee sensitivity have been on the basis of inhalation rather than ingestion. To follow up this lead we tested our patient with an extract of roasted coffee and obtained a negative reaction. The temperature in the roasting ovens is about 400° F. (244° C.). This negative reaction to extract

of roasted coffee shows that the roasting process successfully destroys the allergenic fraction of the coffee bean. All our patients stated they could freely imbibe an infusion of roasted coffee without the production of allergic symptoms.

Patient 3 was also available for study. He was a man, aged 22, who began work in the office of the coffee-roasting plant in April, 1947. In the late summer of 1947, he developed symptoms of perennial allergic rhinitis which persisted until first seen by us in April, 1949. Some 6 weeks prior to April, 1949, he developed recurring asthmatic attacks which rapidly became more severe and frequent. After the coffee-dust exposure situation was corrected about June, 1949, this man and the other office workers have remained symptom-free.

TABLE II. PATIENT 7. SCRATCH AND PASSIVE TRANSFER TESTS WITH COFFEE AND CASTOR BEAN EXTRACTS

DIRECT TESTS ON BACK. SCRATCH METHOD (11/23/49)	
1. Green coffee dust	+++
2. Green coffee bean	+++
3. Castor bean allergen CB-1A (1:100,000 dilution)	++++
4. House dust	++++
5. Ragweed	+++
6. Extract new burlap bag	Negative
ALL EXTRACTS BOILED IN WATER BATH 6 MINUTES (12/19/49)	
1. Green coffee dust	++
2. Green coffee bean	+++
3. Castor pomace (1:10,000 dilution)	++++
ALL EXTRACTS AUTOCLAVED AT 15 LBS. PRESSURE FOR 20 MINUTES (12/22/49)	
1. Green coffee dust	++
2. Green coffee bean	+++
3. Castor pomace	+++
(2/27/50)	
1:10 Extract of roasted coffee	Negative

PASSIVE TRANSFER TESTS (1/5/50)	
1. Green coffee dust (1:100 dilution)	++
2. Green coffee bean (1:100 dilution)	++
3. CB-1A (1 mγ* per each 0.025 ml. saline)	++ (wheal 10 × 10 mm.)
4. CB-1A 10 mγ per each 0.025 ml. saline)	+++ (wheal 20 × 15 mm.)
5. CB-1A (100 mγ per each 0.025 ml. saline)	++++ (wheal 30 × 15 mm.)
6. Green coffee dust (1:100 dilution; autoclaved)	++
7. Green coffee bean (1:100 dilution; autoclaved)	++
8. House dust	+++
9. Ragweed 1:1000 dilution)	Negative
10. Ragweed 1:100 dilution)	+
11. Roasted coffee extract (1:10 dilution)	Negative

*Milligamma (mγ) = 0.000,001 milligram.
All extracts gave negative control tests.

As shown by Table III, the direct tests done on this patient duplicate those done on Patient 7 (Table II). Passive transfer tests using serum from Patients 3 and 7 merely corroborate the results of direct testing. One point in the passive transfer tests is worthy of notice, namely, the exquisite sensitivity of these patients to the potent castor bean fraction CB-1A. As Tables II and III show, the tests with these very weak CB-1A dilutions on the recipients' sensitized skin were as large as one would expect in most instances of direct testing with less potent allergens. In particular, high dilutions of castor bean allergen gave much larger tests than the coffee bean extract. Although this study of these patients' reactions to various tests failed to achieve our purpose, namely, to prove the presence of castor bean allergen in green coffee dust, we report it at some length because of our finding of the amazing heat stability of the dominant allergen in the coffee bean.

TABLE III. PATIENT 3. SCRATCH AND PASSIVE TRANSFER TESTS WITH COFFEE AND CASTOR BEAN EXTRACTS

DIRECT TESTS ON BACK. SCRATCH METHOD (5/5/49)	
1. Green coffee dust	+++
2. Green coffee bean	++++
3. Castor bean allergen CB-1A	++++
4. House dust	+++
5. Extract new burlap bag	Negative
(4/3/50)	
1. Boiled extract green coffee bean	++++
2. Autoclaved extract green coffee bean	+++
3. Extract of roasted coffee (10 per cent)	Negative

PASSIVE TRANSFER TESTS (4/5/50)	
1. Green coffee dust (1:100 dilution)	++
2. Green coffee bean (1:100 dilution)	+++
3. CB-1A 1 mγ per each 0.025 ml. saline	+
4. CB-1A 10 mγ per each 0.025 ml. saline	++
5. CB-1A 100 mγ per each 0.025 ml. saline	+++
6. Boiled extract green coffee bean	+++
7. Autoclaved extract of green coffee bean	++
8. Extract of roasted coffee (1:10 dilution)	Negative
9. House dust	+++

All extracts gave negative control tests.

Our failure to prove the identity of castor bean allergen by indirect evidence prompted discussion of this problem with Dr. Henry Stevens* who was currently engaged in a relevant investigation. At his request a sample of green coffee dust was submitted for examination by the Schultz-Dale technique. Following is the report of this examination by Dr. E. J. Coulson*:

"A 1:10 extract of green coffee dust (Our No. 1501) was made in physiological salt solution with addition of toluene to saturation for preservation: (10 Gm. of No. 1501 mixed with 90 c.c. of 0.9 per cent NaCl, saturated with toluene.) After standing 20 days at room temperature, with occasional mixing, the mixture was filtered through paper.

"The extract was compared with our castor bean allergen, CB-1A, for specificity and potency of this allergen. Uterine muscle from guinea pigs sensitized with CB-1A reacted to the coffee dust extract. The same extract induced no reaction in muscle from normal control animals. Results provided convincing evidence that the coffee-dust extract contained castor bean allergen.

"Estimated equivalence to CB-1A:

> 1:10 extract of green coffee dust (No. 1501) contained castor bean allergen equivalent to 0.14 p.p.m. of CB-1A.
>
> The green coffee dust contained castor bean allergen equivalent to 1.4 p.p.m. of CB-1A."

This, then, is the proof that the green coffee dust examined contained castor bean allergen.

In 1945, Bernton, under the title of "Castor Bean Sensitiveness,"[2] reported the case of a man who developed castor bean sensitivity from exposure to burlap sacks which had contained castor pomace. We recommend Bernton's article to all who read this report. It is the most complete treatise to date on the subject of castor bean sensitivity, with all-inclusive references.

*Allergen Research Division, Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

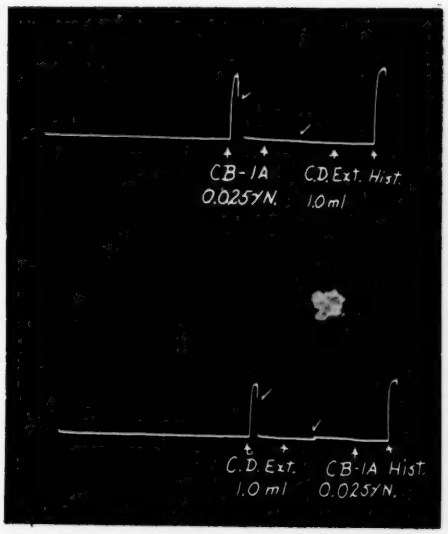

Fig. 1.—Identification of CB-1A in green coffee dust extract. This guinea pig was sensitized with CB-1A. CB-1A induced a contraction in the sensitized uterus and desensitized to CB-1A. (Five ml. of coffee dust extract induced no response in tissues from nonsensitized animals.)

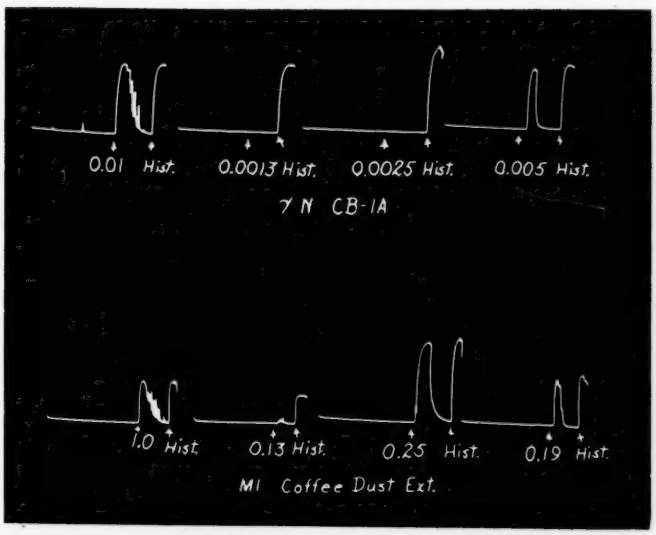

Fig. 2.—Estimation of CB-1A in green coffee dust extract. Each continuous tracing represents a separate uterine strip from an animal sensitized with CB-1A. The contraction induced by 0.19 ml. of coffee dust extract was equivalent to the response induced by 0.005 γ N of CB-1A. CB-1A contains 18.4 per cent nitrogen. Hence, the coffee dust extract contained 0.14 γ CB-1A per ml.

In our opinion, castor bean contains the most potent allergenic fractions known to man. In addition, castor bean contains a powerful toxic albumen, ricin, which rivals cobra venom or diphtheria toxin in potency. Accordingly, ordinary aqueous extracts of castor bean should never be used even for scratch testing; never should castor bean extract of any description be used for direct intracutaneous skin testing. An extract from which the ricin has not been removed will cause more or less severe toxic lymphangitis—even on scratch testing. As for intracutaneous testing, dericinized extracts highly diluted may cause alarming constitutional reactions. For practical purposes, dericinized castor bean extracts may be purchased from any of several commercial firms which sell test materials.

Here follows the most informative reply of Mr. R. L. Beyer, Manager of The Castor & Industrial Soybean Oil Department of Spencer Kellogg & Sons, Inc., to an inquiry regarding the extent of castor bean importation:

"During 1948, the United States imported castorseed for consumption as follows:

COUNTRY	POUNDS
Mexico	4,800
Guatemala	10,000
Salvador	172,380
Haiti	5,792,046
Ecuador	5,141,787
Brazil	289,295,370
Netherlands	700
France	13,426
Siam	2,080,330
Total	302,510,839

"It is obvious from these figures that Brazil is by far the most important source of our castorseed. Haiti and Ecuador also contribute substantially.

"Castorseed crushing mills of importance in the United States are located as follows:

Edgewater, N. J.
Bayonne, N. J.
Jersey City, N. J.
Blue Point, Long Island
Los Angeles, Calif.

"Castor pomace, as far as we know, is used only as a fertilizer. It is particularly popular as a fertilizer for tobacco and for citrus fruits.

"Castorseed from Brazil normally is shipped in 60-kilo. bags made of either caroa fiber or jute fiber. Our Edgewater, N. J., mill quite frequently reconditions these bags and uses them for the shipment of castor pomace. I believe some of the castorseed bags may be resold in the New York market to dealers.

"It does seem possible that bags that contained castor pomace, if carelessly handled, would be possible causes of allergic difficulty for susceptible persons.

"It seems highly unlikely to me that coffee would be shipped in bags that had contained castorseed or castor pomace, because I have been under

the impression that coffee moves in its original bags from Brazil and is customarily shipped in new bags down there."

The report of these 9 cases of castor-bean sensitivity is presented to call attention to a widespread, highly potent allergen which we feel has been somewhat neglected, or at least overlooked. Our discussion shows that thousands of bags of castor bean and castor pomace are in transit annually through our nation. After reaching their destination, many of the bags when empty are sold through junk dealers and put to other uses. Eventually they may come to rest in our homes. What householder is unable, on request, to produce a burlap bag from the basement, attic, or garage? It follows that dericinized extract of castor bean should be included in the routine list of testing substances of every practicing allergist. Its use may reveal the cause of occasional puzzling cases of inhalant allergy.

In 1928, one of us (K. D. F.) was the co-author of an article[3] reporting a large number of cases of asthma caused by castor-pomace dust emanating from a castor bean-crushing mill in east Toledo. It may be of interest to relate that the matter finally found its way into the courts, and that in 1932 the Common Pleas Court, later sustained by the Court of Appeals, ordered a permanent injunction against the processing of castor bean in Toledo. Soon after, the plant was dismantled and castor bean asthma became a rarity in our experience. Occasionally we have since encountered castor bean-sensitive persons whose sensitivity could be traced to previous residence near this mill. However, only recently have we discovered the 9 cases reported herein, whose trouble came from contact with other sources than the former Toledo castor bean-crushing mill. None of these 9 patients ever lived in the vicinity of this mill prior to its dismantling.

SUMMARY

1. Nine cases of sensitivity to the castor bean allergen are reported. The source of contact was dust from burlap bags used (1) in shipping green coffee, or (2) in shipping metal castings. These bags had been contaminated by contact with castor bean or castor pomace.

2. Dericinized castor bean extract should be included in the allergist's routine list of testing materials.

3. Only dericinized castor bean extract should be used for skin testing, and then only by the scratch (dermal) method. Never should even weak dilutions of any type of castor bean extract be used for direct intracutaneous testing.

4. The coffee bean contains a dominant allergenic fraction that is stable on autoclaving for 20 minutes at 15 pounds' pressure, but is inactivated by the commercial roasting process.

REFERENCES

1. Spies, Joseph R., and Coulson, E. J.: The Chemistry of Allergens. VIII. Isolation and Properties of an Active Protein-Polysaccharidic Fraction, CB-1A, From Castor Beans, J. Am. Chem. Soc. **65**: 1720-1725, 1943.
2. Bernton, H. S.: Castor Bean Sensitiveness, J. South. Med. Ass'n **38**: 670-677, 1945.
3. Figley, K. D., and Elrod, R. J.: Endemic Asthma Due to Castor Bean Dust, J. A. M. A. **90**: 79, 1928.

IDENTIFICATION OF CASTOR BEAN ALLERGEN IN GREEN COFFEE*

E. J. Coulson, Joseph R. Spies, and Henry Stevens, Washington, D. C.

THIS report supplements the clinical evidence which led Figley and Rawling[1] to recognize apparent sensitiveness to green coffee dust as actually castor bean allergy. Our collateral interests relevant to identification of castor bean allergen[2] prompted examination of additional specimens of green coffee dust and other coffee products collected from different sources. The results amplify Figley and Rawling's observations[1] and imply that contamination of green coffee with some castor bean derivative is not exceptional.

DESCRIPTION OF SAMPLES

Green Coffee Dusts

Sample T.—Furnished by Dr. Karl D. Figley of Toledo, Ohio, as representative of the material which he used in his clinical studies and described in his report.[1]

Sample C.—Furnished by Dr. Leon Unger of Chicago, Ill., from his stock of various by-products of green and roasted coffee. This sample was identical in appearance with Sample T.

Sample W.—Collected at a coffee roasting plant in Washington, D. C. In appearance it was like Samples T and C, except that it contained a minor proportion of whole and broken beans.

Green Coffee Beans

Sample F.—Selected at random from a collection of samples of cleaned and blended green coffee that had been submitted to the Food and Drug Administration for grading in connection with government purchases. This sample was composed entirely of cleaned, sound, whole beans.

Sample P.—Parchment coffee selected from a specimen collected at an agricultural experiment station in Guatemala, by the Office of Foreign Agricultural Relations, U. S. Department of Agriculture. Parchment coffee is separated from the coffee cherry by fermentation of the residual cherry pulp, washing in water, and drying. At this stage of processing for export, the coffee bean is enclosed in two membranes: the adherent silverskin (spermoderm), and a surrounding, friable shell suitably called the parchment (endocarp). The specimen of parchment coffee, from which beans with unbroken parchment were selected for Sample P, provided green coffee that had not been exposed directly or indirectly to any contaminant. Sample P was dissected and separated into three parts: the parchment membrane, the silverskin, and the coffee bean.

Sample G.—Cleaned, green coffee beans obtained especially for this investigation by the Office of Foreign Agricultural Relations from Instituto Agro-

*Contribution from the Allergen Research Division, Bureau of Agricultural and Industrial Chemistry, U. S. Department of Agriculture, Washington 25, D. C.

pecuario Nacional, Guatemala, and certified by Rolland C. Lorenz, Director, to be "absolutely free of any contact with castor beans."

Sample GP.—Parchment coffee from the same source as Sample G.

Powdered Soluble Coffee

Sample SC-1.—Brand A.

Sample SC-2.—Brand B.

Powdered soluble coffees are made by rapid drying of a concentrated and filtered water extract of roasted coffee. Accordingly, Samples SC-1 and SC-2 represented a substantial concentration of the water extract of roasted coffee.

PREPARATION OF TEST SOLUTIONS

One part by weight of each of the green coffee dusts was extracted with 9 parts of physiologic saline solution, saturated with toluene. The 1:10 extracts were filtered through filter paper and used for the Dale tests without further treatment. These extracts contained from 0.6 to 0.7 mg. total nitrogen and from 0.4 to 0.5 mg. protein nitrogen (phosphotungstic acid) per ml.

Green coffee beans were ground to pass a 20-mesh sieve before extraction. Saline 1:10 extracts of ground beans contained from 1.3 to 1.9 mg. total nitrogen and from 0.8 to 1.2 mg. protein nitrogen per ml. One preparation of coffee bean extract (Sample F) contained a nonspecific muscle irritant. This was completely removed by dialysis of the extract for 15 hours in running water. Before use in the Schultz-Dale tests, the dialyzed extract was equilibrated with Tyrode solution. About 50 per cent of the nitrogenous components of the extract was removed by dialysis. Experiments with CB-1A had shown that less than 10 per cent of the allergen would be lost under comparable conditions.[2]

A 1:10 extract of the parchment membrane from Sample P contained 0.06 mg. total nitrogen and 0.03 mg. protein nitrogen per ml. A 1:20 extract of silverskin from Sample P contained 0.4 mg. total nitrogen and 0.3 mg. protein nitrogen per ml.

Ten grams of each of the powdered soluble coffees was dissolved in hot water, cooled, and made up to 50 ml. with cold water. The 1:5 dilutions of Samples SC-1 and SC-2 contained 6.9 and 3.2 mg. total nitrogen and 4.6 and 2.1 mg. protein nitrogen per ml., respectively. Both preparations were dialyzed and equilibrated with Tyrode solution before use. About 80 per cent of the nitrogenous components of each preparation was removed by dialysis.

IDENTIFICATION AND DETERMINATION OF CB-1A IN COFFEE PRODUCTS

Identification and determination of the castor bean allergen, CB-1A, in the extracts of coffee products were conducted by Moody's[3] modification of the Schultz-Dale technique as illustrated in Figley and Rawling's report.[1] Each extract was tested first with uterine muscles from nonsensitized guinea pigs to prove the absence of nonspecific, muscle irritants. The smallest dose of each extract required to induce anaphylactic contraction of uterine muscle segments from an animal sensitized with CB-1A was then determined. This dose was

compared with the smallest dose of CB-1A required to produce an equivalent response in uterine tissue from the same animal. From this comparison the approximate concentration of CB-1A in the extract was calculated. Finally, the capacities of the extract and of CB-1A to desensitize to each other were tested for each sample. Without exception, extracts that induced anaphylactic contractions in CB-1A-sensitized muscle desensitized the tissue to subsequent tests with maximal doses of CB-1A. Likewise, reaction with and desensitization to CB-1A desensitized the tissue to subsequent maximal doses of the reactive extracts. On the other hand, nonreactive extracts did not desensitize to minimal doses of CB-1A.

The sensitivity of the quantitative Dale technique is dependent on 3 factors: (1) the sensitivity of the muscle tissue to CB-1A; (2) the concentration of the extract; and (3) the volume of the extract that may be used satisfactorily in the test. For example, if a muscle tissue is sensitive to a minimal dose of 0.011 μg CB-1A and is not responsive to a dose of 5 ml. of a 1:10 extract of coffee beans, then the extract contains less than 0.002 μg CB-1A per ml., and the original sample contains less than 0.02 μg CB-1A per Gm. The limit of sensitivity for this test would be 0.02 p.p.m. of CB-1A.

Previous work in this laboratory[4] has shown that the sensitizing dose of CB-1A is more than 25 times larger than the shock dose. The present work shows that the Schultz-Dale method is more than 200 times as sensitive for detecting CB-1A as by demonstration of anaphylactic shock and more than 6,000 times as sensitive as by demonstration of sensitization.

The maximal dosage of extract used in these tests was 5 ml. (in 50 ml. Dale baths) except in 1 instance; Sample G was tested at both 5 ml. and 10 ml. dosage levels. Specifically reactive dosages for the green coffee dust extracts ranged from 0.02 to 0.5 ml. Dosages up to 10 ml. induced no response in tissues from control animals.

RESULTS

Table I records the castor bean allergen content of various coffee products calculated as p.p.m. of CB-1A in the original sample. The results are averages of duplicate or triplicate determinations. The last column records the limit of sensitivity of the test for detecting CB-1A in the sample.

Each of 3 green coffee dust samples examined contained castor bean allergen. Concentration of the allergen, calculated as CB-1A, ranged from 1 to 5 p.p.m.

The 1 sample of cleaned, green coffee beans obtained from commercial sources (Sample F) contained castor bean allergen equivalent to 0.08 p.p.m. of CB-1A. It seemed pertinent to determine whether the castor bean allergen in this sample was a surface contaminant or whether it permeated the whole bean. Accordingly, 20 Gm. of the whole bean was washed 4 times with 25 ml. portions of saline. The combined washings were filtered and concentrated in vacuo to about 30 ml. This concentrated extract was dialyzed and equilibrated with Tyrode solution. The beans were then thoroughly washed in running water for 30 minutes, dried, ground, and extracted in the usual manner.

The dialyzed washings from the original whole beans contained allergen equivalent to 0.6 μg CB-1A which represented 0.03 p.p.m. in the whole beans. On the other hand, no castor bean allergen could be detected in the extract from the washed and ground beans. Evidently, the castor bean allergen was a surface contaminant.

Castor bean allergen was not detectable in extracts from any of the green coffee products obtained from the experiment station in Guatemala. Hence, green coffee does not contain antigen similar to CB-1A.

No castor bean allergen was detected in the powdered soluble coffee.

Attempts to demonstrate castor bean allergen in the green coffee dusts by sensitization were unsuccessful. Uterine muscles from animals sensitized with alum-precipitated coffee dust extracts reacted with the dust extracts but none of them reacted with 0.5 mg. doses of CB-1A. These results coincide with the observation that detection of CB-1A by sensitization is less sensitive than detection by demonstration of anaphylaxis in sensitized animals or tissues.

TABLE I. RESULTS OF ASSAY OF CASTOR BEAN ALLERGEN (CB-1A) IN COFFEE PRODUCTS

SAMPLE NO. AND DESCRIPTION	CB-1A FOUND P.P.M.	LIMIT OF SENSITIVITY P.P.M.
Green Coffee Dusts		
Sample T	1.4	
Sample C	1.0	
Sample W	5.0	
Commercial Green Coffee—Sample F		
Untreated beans, ground and extracted	0.08	
Saline extract of whole beans	0.03	0.004
Washed beans, ground and extracted	None	0.03
Parchment Coffee—Sample P		
Parchment membrane (endocarp)	None	0.03
Silverskin (spermoderm)	None	0.08
Bean (endosperm and embryo)	None	0.03
Green Coffee From Guatemala Experiment Station		
Sample G (cleaned green coffee)	None	0.01
Sample GP (coffee in parchment)	None	0.02
Powdered Soluble Coffee		
Sample SC-1 (Brand A)	None	0.01
Sample SC-2 (Brand B)	None	0.01

DISCUSSION

Unequivocal evidence of castor bean allergen as a contaminant of green coffee has been established. The 3 samples of green coffee dust and 1 sample of cleaned, green coffee beans, in each of which the castor bean allergen was identified, were from green coffee delivered to, or offered for delivery to, wholesale purchasers in Toledo, Chicago, and Washington. Conditions of collection of these samples permit the inference that the 4 samples were not from the same lot or shipment, but evidence to support that inference is lacking. The place of origin and relevant history is known only for the 3 samples of green coffee supplied by the Office of Foreign Agricultural Relations. None of them contained detectable castor bean allergen.

Detection of castor bean allergen in green coffee dust also implies the presence of the active toxalbumin, ricin, of castor bean. In the sensitization experiments animals injected with 2 ml. of the coffee dust extracts showed no evidence of ricin toxicity during the incubational period. However, the dosage used for sensitization would not have contained more than one-tenth of a lethal dose of ricin and, accordingly, would not be likely to induce recognizable symptoms of ricin toxicity. This speculative calculation was based on the assumption that ricin might accompany the castor bean allergen in the proportion found in castor bean. Actually, neither the origin nor identity of the castor bean contaminant is known. Nevertheless, it would be reasonable to assume that ricin would be present whether the contaminant were castor bean or castor pomace.

Extensive examinations of roasted coffee did not appear to be justified by available clinical evidence. Moreover, the experiments recorded here showed that the castor bean contaminant detected in cleaned green coffee was on the surface of the unroasted beans. Observation of the conventional commercial roasting process showed that the surfaces of individual beans are thoroughly exposed to radiation from bare, red-hot, heating elements at a temperature which causes ignition of loosened particles of coffee dust. Presumably, the roasting process would completely inactivate superficial castor bean contaminant. Examination of 2 brands of powdered, soluble coffee failed to reveal any trace of castor bean allergen. However, there was no evidence that these products were derived from contaminated coffee.

SUMMARY

Castor bean allergen was identified in 3 samples of green coffee dust from different coffee roasting plants. Castor bean allergen was also found in 1 sample of cleaned, green coffee beans from a commercial source.

No castor bean allergen was detected in samples of parchment coffee or cleaned, green coffee beans which were produced at a Guatemalan experiment station and were known to have had no contact with castor bean.

Available evidence indicates that hazards resulting from contamination of green coffee with a castor bean derivative are significant only to those who are exposed to green coffee.

REFERENCES

1. Figley, K. D., and Rawling, F. F. A.: Castor Bean: An Industrial Hazard as a Contaminant of Raw Coffee Dust and Used Burlap Bags, J. ALLERGY **21**: 545, 1950.
2. Spies, J. R., and Coulson, E. J.: The Chemistry of Allergens. VIII. Isolation and Properties of an Active Protein-Polysaccharidic Fraction, CB-1A, From Castor Beans, J. Am. Chem. Soc. **65**: 1720, 1943.
3. Moody, P. A.: Delicacy of Differentiation by the Schultz-Dale Test as Revealed by End-Point Determination on Rodent Sera, J. Immunol. **39**: 113, 1940.
4. Coulson, E. J., Spies, J. R., Stevens, H., and Shimp, J. H.: The Immunochemistry of Allergens. X. Anaphylactogenic Properties of Allergenic Fractions From Castor Bean, J. ALLERGY **21**: 34, 1950.

EVALUATION OF THERAPEUTIC SUBSTANCES EMPLOYED FOR THE RELIEF OF BRONCHOSPASM

VII. Combinations of Diphenhydramine With Ephedrine and Aminophylline*

Hyman J. Rubitsky, M.D.,† J. Aaron Herschfus, M.D.,‡
Leon Levinson, M.D.,§ Elliott Bresnick, M.D.,**
and Maurice S. Segal, M.D.,†† Boston, Mass.

WE HAVE previously described[1] a method for the evaluation of antiasthmatic agents in terms of their ability to protect sensitive asthmatic subjects against histamine- and methacholine-induced dyspnea and bronchospasm, the latter being measured as changes in vital capacity. Data obtained with various anticholinergic, antihistaminic, and sympathomimetic agents, as well as with aminophylline, have been presented elsewhere.[2] The present report deals with the effect of various combinations of such agents, administered simultaneously by mouth.

METHODS

Reproducible decreases in vital capacity, usually associated with dyspnea and wheezing and occasionally with cough, may be induced in sensitive asthmatic individuals by administration of histamine or methacholine. Following the intravenous administration of suitable doses of histamine (0.01 to 0.05 mg. of histamine base) or methacholine (0.1 to 0.5 mg. of methacholine chloride), wheezing and dyspnea become evident after about 20 seconds. The response reaches its maximum 30 to 60 seconds after administration of the bronchospastic substance, and rapidly fades away, the vital capacity usually returning to resting levels within 5 minutes. The effect of any "protecting agent" may be measured by the alteration in this response to histamine or methacholine which follows administration of the protecting substance. We have defined the degree of protection in terms of the following equation:

$$P = \frac{C - E}{C} \times 100$$

where: P = degree of protection in per cent,

C = drop in vital capacity induced by histamine or methacholine prior to administration of the protecting agent, and

E = drop in vital capacity similarly induced after the protecting agent has been given.

The data herein presented are the averages of 4 such "protection studies." The same 4 individuals participated in each group of experiments.

*Aided by a grant from the United States Public Health Service.

†Former Research Fellow in Medicine, Tufts College Medical School.
‡Research Fellow in Medicine, Tufts College Medical School.
§Assistant in Medicine, Tufts College Medical School.
**Out-Patient Physician, Boston City Hospital; Assistant in Medicine, Tufts College Medical School.
††Director, Department of Inhalational Therapy, Boston City Hospital; Assistant Professor of Medicine, Tufts College Medical School.

We feel that these averages are of greater significance than single studies, where wide variations are not infrequent.

RESULTS

1. *Diphenhydramine and ephedrine.*—A group of 4 sensitive asthmatic subjects, in whom drops in vital capacity are easily induced by intravenous administration of histamine, were studied after the oral administration of diphenhydramine hydrochloride, 50 mg., ephedrine sulfate, 25 mg., and the 2 agents combined. The results are presented in Fig. 1. It may be seen by reference to the graph that the combination of the 2 agents demonstrated slightly greater antihistaminic activity than did diphenhydramine or ephedrine alone; no semblance of arithmetic summation is present.

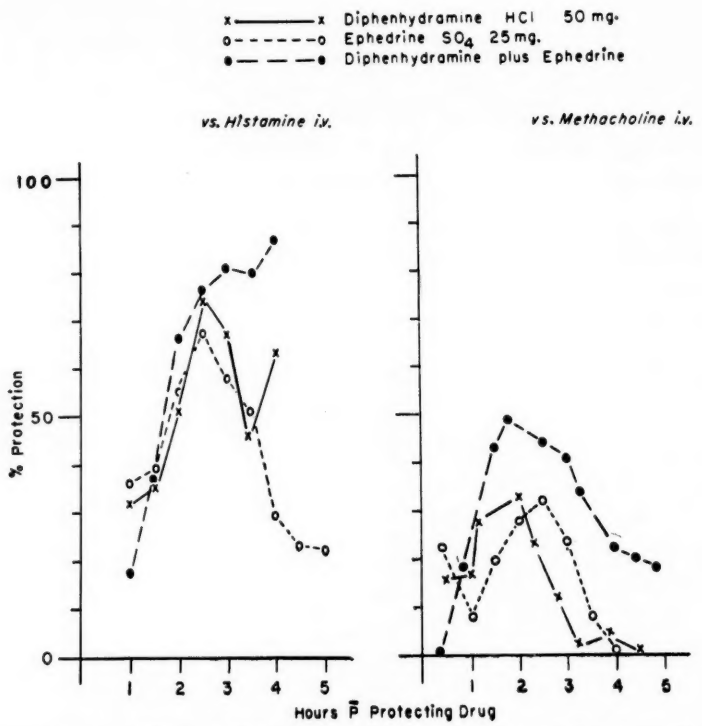

Fig. 1.—The protective ability of diphenhydramine hydrochloride, ephedrine sulfate, and the combination of these agents, against the bronchospastic effects of histamine and methacholine.

In another group of individuals, the same drugs were tested against methacholine-induced changes in vital capacity. Here, again, the combination is slightly more effective than either agent involved.

2. *Diphenhydramine and aminophylline.*—Results of the administration of diphenhydramine hydrochloride, 50 mg., and aminophylline, 200 mg., against histamine-induced dyspnea and bronchospasm are presented in Fig. 2, *A*. The combination displays greater antihistaminic activity than does either of its constituents. No such summation occurred against methacholine-induced alterations in vital capacity (Fig. 2, *B*).

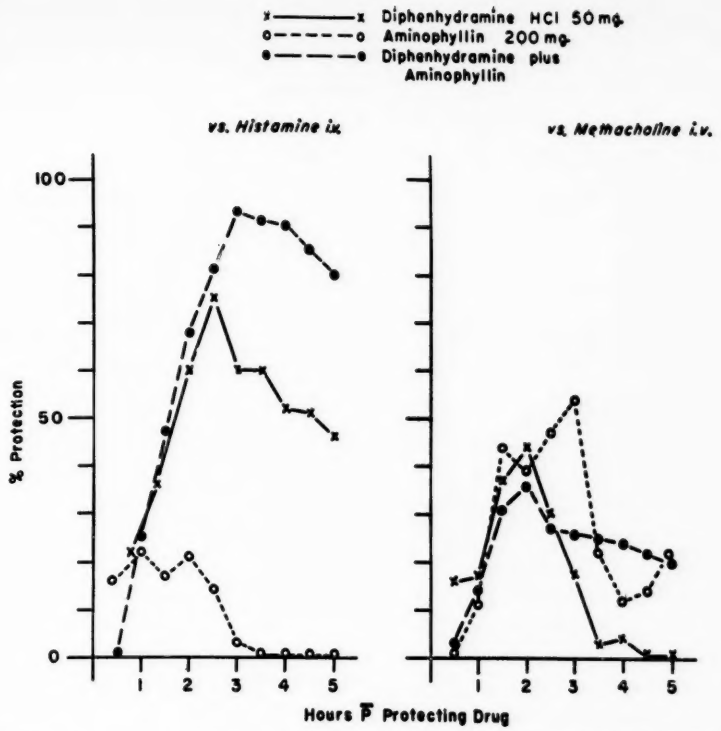

Fig. 2.—The protective ability of diphenhydramine hydrochloride, aminophylline, and the combination of these agents, against the bronchospastic effects of histamine and methacholine.

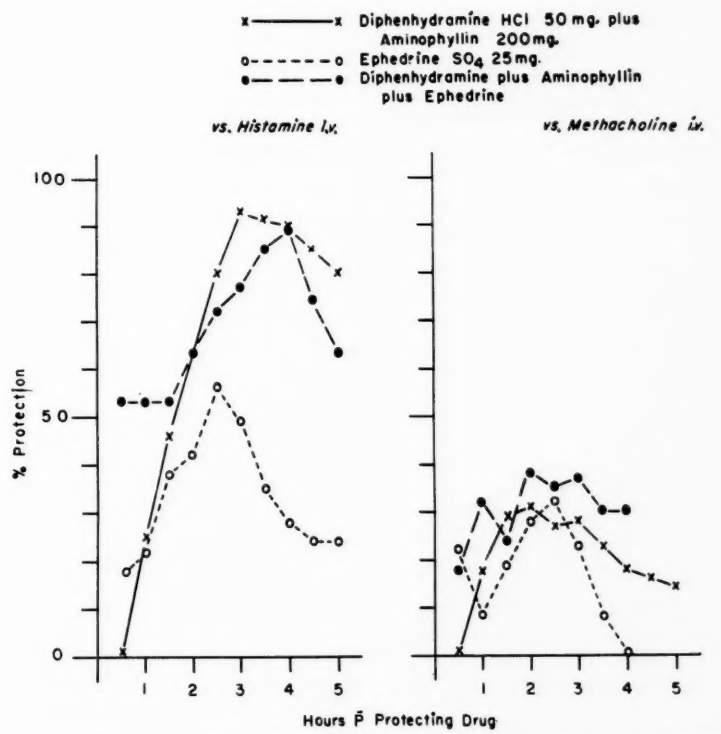

Fig. 3.—The protective ability of diphenhydramine hydrochloride plus ephedrine sulfate, with and without the further addition of aminophylline, against the bronchospastic effects of histamine and methacholine.

3. *Diphenhydramine, ephedrine, and aminophylline.*—When diphenhydramine hydrochloride, 50 mg., ephedrine sulfate, 25 mg., and aminophylline, 200 mg., were administered together by mouth to asthmatic subjects in the same manner, little or no additive effect could be demonstrated against either histamine- or methacholine-induced changes in vital capacity. The results are presented in Fig. 3.

COMMENT

It is common clinical practice in the management of patients with bronchial asthma to prescribe a combination of various antiasthmatic agents, with the expectation that the activity of each drug will be added to that of the others. We have tested this premise in terms of antihisaminic and anticholinergic protective activity in man under laboratory conditions and find that it is apparently not possible significantly to improve the anticholinergic activity of diphenhydramine, 50 mg., by the addition of ephedrine, 25 mg., and/or aminophylline, 200 mg., although slight increases may occur. The combination of diphenhydramine and aminophylline appears to exert a somewhat greater antihistaminic effect than does diphenhydramine alone; no such potentiation occurs with diphenhydramine and ephedrine.

In general, each combination appears to retain the antihistaminic and anticholinergic properties of its most potent component.

SUMMARY

The antihistaminic and anticholinergic protective capacity in man of various combinations of diphenhydramine, ephedrine, and aminophylline is presented.

Combinations of these agents retain the antihistaminic and anticholinergic activity of the most potent ingredient. Aminophylline appears to increase the antihistaminic effect of diphenhydramine, but nothing approaching arithmetic summation has been seen.

REFERENCES

1. Levinson, L., Beakey, J. F., Bresnick, E., and Segal, M. S.: Evaluation of Therapeutic Substances Employed for the Relief of Bronchospasm. II. Historical Development and Methods, Ann. Allergy **6**: 705, 1948.
2. Segal, M. S.: The Management of the Patient With Severe Bronchial Asthma, Springfield, Ill., 1950, Charles C Thomas, Publisher.

Editorial

FOOD ALLERGY

There is perhaps no field of medicine in which more divergent views are held than in that of allergy to foods. It would seem worth while, therefore, to outline some procedure by which a better understanding of the subject could be obtained.

One difficulty in the field is that most manifestations ascribed to food allergy are common to many other conditions, actual or immaginary. Attitudes and beliefs regarding foods, whether or not they are based on physiologic effects, dependent on or independent of psychic influences, stem, in part at least, from centuries of lore, national, religious, racial, regional—and medical. The manifestations claimed by some to be of allergic origin are not only numerous but extremely diverse, so much so that there is hardly an ache or a twinge that may not fall within the purview of the allergist. The *nature* of these reactions, therefore, may give no clue as to the role played by allergy. Indirect tests can be regarded as valid only after they have been shown to be so in instances of *proved* allergy to foods. This remains to be done. Therefore, the use of procedures such as the leukopenic index, changes in the number of circulating eosinophils, or skin tests cannot give us the information we need.

Although it is clearly not sufficient to say that an allergic mechanism operates because a certain reaction follows the ingestion of one or more foods, the demonstration of a cause and effect relationship is nevertheless essential. This is the first step—a difficult one because no procedure can be relied upon in which the patient suspected of food allergy can identify the substance under test by taste, smell, texture, or color. The food should be completely disguised by some means or other, and perhaps it is best given in capsules or by stomach tube. Other foods given in the same manner should fail to cause any reaction. Furthermore, the reaction should be consistently reproducible as regards type and the time of its occurrence. Once these criteria have been met, a cause and effect relationship would appear to have been established, and it would seem reasonable to ascribe the reaction to an allergic mechanism. Such a conclusion is not strictly logical, however, because a cause and effect relationship is not solely peculiar to allergic mechanisms, however much we as allergists may see fit to regard it so.

According to immunologic theory, allergic reactions arise from the interaction of the allergen with antibody fixed to tissue or in close proximity to it. Clear evidence for an allergic mechanism is readily found in many patients with asthma and hay fever, and it would appear reasonable to find similar evidence of an allergic mechanism in a patient who is allergic to one or more foods. If present-day theory requires modification, evidence should be forthcoming to show that the theory in modified form is valid. How is an allergic mechanism to be demonstrated in the patient whose fatigue is attributed to allergy to corn-

starch? Skin reactions to corn may be negative and skin-sensitizing antibody absent. It would appear impossible at present to carry the investigation of such a case beyond the attempt to demonstrate a cause and effect relationship.

Nevertheless, much can be done on this problem. A close study of a relatively small number of carefully selected patients having indubitable allergy to foods, as judged by the type of criteria given above, would go far toward clarifying the subject and giving us a useful understanding of allergic reactions to foods. Such a study might include, in addition to those studies mentioned, quantitative tests for skin sensitivity and skin-sensitizing antibody, determination of the dosage required to produce a reaction, the interval required before the reaction takes place, the duration of the reaction, and something might also be learned concerning the behavior of the white cells, the eosinophils, and the value of x-ray studies. All this is tantamount to saying that we must learn far more about what appears to be familiar before we can effectively tackle the problems that face us in food allergy. The experience gained could then be applied to other patients in whom the role played by allergy can only be a matter of conjecture today.

F. C. Lowell

Book Reviews

THE ANTIHISTAMINICS, THEIR CLINICAL APPLICATION, by Samuel M. Feinberg, Saul Malkiel, and Alan R. Feinberg, Chicago, 1950, The Year Book Publishing Co., 231 pp., $4.00.

There are few fields of medicine in which summation and critical evaluation of recent developments are more needed than in that of histamine antagonists. Not only the general practitioner but also the average allergist who uses these drugs daily has been so confused by the claims of the manufacturers for a score of new compounds introduced in the past five years that choice among the group is guided by habit rather than rational considerations. The many reports of clinical evaluation of various antihistaminics lend themselves poorly to exact comparisons because of variations in the method of use and of expressing results observed. This book offers an interpretation of the extensive literature backed and amplified by tremendous personal experience in the field. The sections dealing with the comparison of the effects of the individual drugs and the choice of medications in various conditions are particularly valuable.

The chapters on chemistry, pharmacology, and experimental studies are useful for reference, as is the tabulation of proprietary compounds and dosage forms. The bibliography of 586 references, while intended to be selective rather than inclusive, offers ample guidance to those who wish to consult the original literature. The evidence on points which remain unsettled is carefully summarized and interpreted conservatively.

This book is heartily recommended to all who have occasion to prescribe these drugs.

PSYCHOSOMATIC MEDICINE, ITS PRINCIPLES AND APPLICATIONS, by Franz Alexander, M.D., New York, 1950, W. W. Norton and Co., 288 pp., $4.00.

Opinion is divided among allergists as to whether the psychosomatic approach to diseases of allergy has been neglected or overemphasized. For those desiring an introduction to these methods, the present volume offers a simple exposition of psychosomatic principles and their applications to various diseases, of which asthma, urticaria, and angioedema are of special interest to the allergist. In the discussion of asthma, allergic factors are considered of essentially equal importance with emotional stresses; the role of infection is ignored.

While the factors of heredity and past disease or injury are considered parts of the etiologic picture, an attempt is made to relate various disease entities to specific forms of psychodynamic stress, rather than considering them as the reactions of varied somatic types to psychic stress in general. The average allergist would probably be more receptive to the thesis that asthma may result from the effect various stresses on a certain type of hereditary and chemical constitution than the view of Dr. Alexander that it results specifically from an excessive unresolved dependence on the mother.

The discussions of neural and hormonal mechanisms of disease are less precise than those of the purely psychic. The works of Selye and of Long are described but scarcely integrated into the whole. The failure of the chapters on asthma and on rheumatoid arthritis to mention the adrenal corticosteroids leaves an impression that the book is already outdated.

Announcements

THREE-DAY COURSE IN MOLD AND POLLEN IDENTIFICATION

An intensive course in identification of molds and pollen is offered on Feb. 2, 3, and 4, 1951, at the Cornell Medical College preceding the annual meeting of the AMERICAN ACADEMY OF ALLERGY. Although the major portion of the time will be given to molds, pollen identification will also be covered adequately. Professor Clyde Christensen of the University of Minnesota, with several assistants, will teach the mold work, while O. C. Durham, chief botanist of Abbott Laboratories, will be in charge of the pollen instruction. The course is organized by the Subcommittee on Molds and is given under the auspices of the Research Council and the Committee on Education of the AMERICAN ACADEMY OF ALLERGY. Registration is limited. The fee is $35.00. Applications may be sent to Dr. Samuel M. Feinberg, 185 North Wabash Avenue, Chicago 11, Ill.

CLINICAL TRAINING IN ALLERGY

NORTHWESTERN UNIVERSITY MEDICAL SCHOOL

Two fellowships are available for 1951 for training in allergy. Fellowships are for a one-year period and include clinical and investigative experience. Preference is given to those who have or intend to complete their board requirements in internal medicine or pediatrics. The stipend is $2,400 to $3,600. For further information write to Dr. Samuel M. Feinberg, Northwestern University Medical School, Chicago 11, Ill.

AUTHORS INDEX

A

ARBESMAN, CARL E., NETER, ERWIN, AND BECKER, CHARLES F. The effect of Pyribenzamine, Neohetramine, and rutin on reversed anaphylaxis in guinea pigs, 25

B

BAER, RUDOLF L. (*See* WHITE AND BAER), 344

BALDWIN, HORACE S. Cardiorespiratory function in relation to asthma and emphysema. Viewpoint of the allergist, 349

BECKER, CHARLES F. (*See* ARBESMAN, NETER, AND BECKER), 25

BLACK, J. HARVEY, AND HOLMAN, JAMES. Treatment of respiratory allergy in children by oral administration of dust and pollen extract, 148

BLUMSTEIN, GEORGE I. (*See* TUFT AND BLUMSTEIN), 326

BOGER, WILLIAM P. (*See* RISMAN AND BOGER), 414

BOOKMAN, RALPH. Kaposi's varicelliform eruption: report of a case treated with aureomycin and some observations regarding the course of the underlying skin disease, 68

BOYD, LINN J. (*See* MCGAVACK, SHEARMAN, WEISSBERG, FUCHS, SCHULMAN, CHEVALLEY, DREKTER, AND BOYD), 353

BRESNICK, ELLIOTT. (*See* RUBITSKY, HERSCHFUS, LEVINSON, BRESNICK, AND SEGAL), 559

BROWN, BERNARD T. (*See* WISEMAN, BROWN, AND GANDIA), 199

BROWN, RAYMOND A. (*See* CAMPBELL, CANN, FRIEDMAN, AND BROWN), 519

C

CAMPBELL, DAN H. (*See* MILLER AND CAMPBELL), 522

—, CANN, JOHN R., FRIEDMAN, TOWNSEND B., AND BROWN, RAYMOND A. Reagic serum fractions obtained by the electrophoresis-convection method, 519

CANN, JOHN R. (*See* CAMPBELL, CANN, FRIEDMAN, AND BROWN), 519

CARRYER, HADDON M., AND CODE, CHARLES F. The effect of cortisone upon the release of histamine during in vitro hemolytic reactions in rabbit blood, 310

— AND —. The effect of tripelennamine hydrochloride (Pyribenzamine) on the release of histamine during in vitro hemolytic reaction in rabbit blood, 314

—, KOELSCHE, GILES A., PRICKMAN, LOUIS E., MAYTUM, CHARLES K., LAKE, CLIFFORD F., AND WILLIAMS, HENRY L. The effect of cortisone on bronchial asthma and hay fever occurring in subjects sensitive to ragweed pollen, 282

CAVELTI, PHILIP A. Complement fixation studies in allergy, 532

CAZORT, ALAN G. Clinical experience with objective diagnostic tests in corn sensitivity, 512

CHAIT, ROBERT A., AND WALZER, MATTHEW. A technique for studying the nasal absorption of allergens in human beings, 153

CHEVALLEY, JACQUELINE. (*See* MCGAVACK, SHEARMAN, WEISSBERG, FUCHS, SCHULMAN, CHEVALLEY, DREKTER, AND BOYD), 353

CHOBOT, ROBERT, DUNDY, HAROLD D., AND PACELLA, B. L. The incidence of abnormal electroencephalographic patterns in allergic children, 334

CHRISTENSEN, CLYDE M. (*See* SWAEBLY, CHRISTENSEN, AND GRAHEK), 404

—. Intramural dissemination of spores of *Hormodendrum resinae*, 409

CLARK, WILLIAM G., AND MACKAY, EATON M. (with the technical assistance of JORDAN, MARY L.) Effect of flavonoid (vitamin P-like) substances on histamine toxicity, anaphylactic shock, histamine-enhanced capillary permeability to dye, and bleeding time; with data on the toxicity of flavonoids, 133

CODE, CHARLES F. (*See* CARRYER AND CODE), 310, 314

COHEN, SHELDON G. (*See* CRIEP, MAYER, AND COHEN), 373

COOKE, ROBERT A. (*See* SHERMAN AND COOKE), 63

COULSON, E. J., SPIES, JOSEPH R., AND STEVENS, HENRY. Identification of castor bean allergen in green coffee, 554

COULSON, E. J., SPIES, R., STEVENS, H., AND SHIMP, JAMES H. The immunochemistry of allergens. X. Anaphylactogenic properties of allergenic fractions from castor bean, 34
CREDILLE, BARNEY. A pollen-counting guide, 78
CRIEP, LEO H., MAYER, LLOYD D., AND COHEN, SHELDON G. Effect of x-ray radiation on hypersensitiveness, 373

D

DE VRIES, J. A. (*See* HERBERT, DE VRIES, AND ROSE), 12
DREKTER, I. J. (*See* MCGAVACK, SHEARMAN, WEISSBERG, FUCHS, SCHULMAN, CHEVALLEY, DREKTER, AND BOYD), 353
DUNDY, HAROLD D. (*See* CHOBOT, DUNDY, AND PACELLA), 334
DURHAM, OREN C. Report of the Pollen Survey Committee of the American Academy of Allergy for the season of 1949, 442

F

FARMER, LAURENCE, AND ROHDENBURG, GEORGE L. Histamine induced cardiovascular lesions, 120
FEINBERG, SAMUEL M. (*See* MALKIEL AND FEINBERG), 525
FIGLEY, KARL D., AND RAWLING, FRANK F. A. Castor bean: an industrial hazard as a contaminant of green coffee dust and used burlap bags, 545
— AND —. Clinical experience in corn sensitivity, 510
FRIEDLAENDER, ALEX S. (*See* FRIEDLAENDER AND FRIEDLAENDER), 303
FRIEDLAENDER, SIDNEY, AND FRIEDLAENDER, ALEX S. The effect of pituitary adrenocorticotrophic hormone (ACTH) on histamine intoxication and anaphylaxis in the guinea pig, 303
FRIEDMAN, TOWNSEND B. (*See* CAMPBELL, CANN, FRIEDMAN, AND BROWN), 519
FRIES, JOSEPH H., AND GLAZER, ISRAEL. Studies on the antigenicity of banana, raw and dehydrated, 169
FUCHS, ABNER M. (*See* MCGAVACK, SHEARMAN, WEISSBERG, FUCHS, SCHULMAN, CHEVALLEY, DREKTER, AND BOYD), 353

G

GAENSLER, EDWARD A. Ventilatory tests in bronchial asthma. Evaluation of vital capacity and maximum breathing capacity, 232
GAILLARD, G. EVERETT, Poison ivy. A summary of 100 cases treated with aqueous (alum precipitated pyridine) extract, 55
—. The aphid—an insect allergen, 386
GANDIA, ANTONIO G. (*See* WISEMAN, BROWN, AND GANDIA), 199
GLAZER, ISRAEL. (*See* FRIES AND GLAZER), 169
GOODELL, HELEN (*See* WOLF, HOLMES, TREUTING, GOODELL, AND WOLFF), 1
GRAHAM, DAVID T., WOLF, STEWART, AND WOLFF, HAROLD G. Changes in tissue sensitivity associated with varying life situations and emotions; their relevance to allergy, 478
GRAHEK, THEODORE A. (*See* SWAEBLY, CHRISTENSEN, AND GRAHEK), 404
GUERRANT, JOHN L., MCCAUSLAND, ALEXANDER, AND SWINEFORD, OSCAR, JR. Asthma with sinus disease. A comparison of radical sinus surgery and conservative treatment, 187

H

HARRIS, LEONARD H. Report of the Subcommittee on Mold Survey of the Research Council, American Academy of Allergy, for the season of 1949, 455
HARRIS, M. COLEMAN, AND SHURE, NORMAN. Sudden death due to allergy tests, 208
HECK, V. MURIEL. (*See* TUFT AND BLUMSTEIN), 326
—. (*See* TUFT, TUFT, AND HECK), 181
HERBERT, P., DE VRIES, J. A., AND ROSE, B. Studies on the effect of the administration of pituitary adrenocorticotrophic hormone (ACTH) to a case of Loeffler's syndrome and a case of tropical eosinophilia, 12
HERSCHFUS, J. AARON. (*See* RUBITSKY, HERSCHFUS, LEVINSON, BRESNICK, AND SEGAL), 559
HOLMAN, JAMES. (*See* BLACK AND HOLMAN), 148
HOLMES, THOMAS H. (*See* WOLF, HOLMES, TREUTING, GOODELL, AND WOLFF), 1

J

JAHIEL, RENÉ. (*See* JAHIEL AND JAHIEL), 102
JAHIEL, RICHARD, AND JAHIEL, RENÉ. Local organ hypersensitivity to autogenous antigens. I. Experimental production of a pneumonitis, 102
JORDAN, MARY L. (*See* CLARK AND MACKAY), 133

K

KAILIN, ELOISE W., ROSSBACH, ELINOR A., AND WALZER, MATTHEW. Factors influencing reagin formation in experimental human sensitization to *Ascaris lumbricoides* antigen. IV. The influence of a previous sensitization on rate of sensitization, 225
KAUFMAN, J. M. (*See* WALDBOTT, KAUFMAN, AND MERKLE), 339

KERN, ARTHUR B. (*See* REISS AND KERN), 160

KOELSCHE, GILES A. (*See* CARRYER, KOELSCHE, PRICKMAN, MAYTUM, LAKE, AND WILLIAMS), 282

L

LAKE, CLIFFORD F. (*See* CARRYER, KOELSCHE, PRICKMAN, MAYTUM, LAKE, AND WILLIAMS), 282

LAST, JULES H. (*See* ROSTENBERG, LAST, AND RODRIQUEZ), 217

LEVAN, PAUL. (*See* PERRY AND LEVAN), 73

LEVINSON, LEON. (*See* RUBITSKY, HERSCHFUS, LEVINSON, BRESNICK, AND SEGAL), 559

LOVELESS, MARY HEWITT. Allergy for corn and its derivatives: experiments with a masked ingestion test for its diagnosis, 500

—. Milk allergy: a survey of its incidence; experiments with a masked ingestion test, 489

M

MACKAY, EATON M. (*See* CLARK AND MACKAY), 133

MCCAUSLAND, ALEXANDER. (*See* GUERRANT, MCCAUSLAND, AND SWINEFORD), 187

MCGAVACK, THOMAS H., SHEARMAN, ANN M., WEISSBERG, JONAS, FUCHS, ABNER M., SCHULMAN, PHILIP M., CHEVALLEY, JACQUELINE, DREKTER, I. J., AND BOYD, LINN J. Newer antihistaminics: III. Some pharmacologic and therapeutic effects of β - (p-methylbenzhydryloxy) - ethyldimethylamine hydrochloride, a derivative of diphenhydramine hydrochloride, 353

MALKIEL, SAUL, AND FEINBERG, SAMUEL M. Effect of slowly absorbing antigen (ragweed) on neutralizing antibody titer, 525

MARSHALL, ROBERT B., JR. (*See* MOSKO AND MARSHALL), 242

MAYER, LLOYD D. (*See* CRIEP, MAYER, AND COHEN), 373

MAYTUM, CHARLES K. (*See* CARRYER, KOELSCHE, PRICKMAN, MAYTUM, LAKE, AND WILLIAMS), 282

MERKLE, K. J. (*See* WALDBOTT, KAUFMAN, AND MERKLE), 339

MILLER, HYMAN, AND CAMPBELL, DAN H. Skin test reactions to various chemical fractions of egg white and their possible clinical significance, 522

MITCHELL, JOHN H. Food allergy: acute vs. chronic, 514

MOSKO, MILTON M., AND MARSHALL, ROBERT B., JR. A study of the effect of various drugs on the wheeling reaction, 242

N

NETER, ERWIN. (*See* ARBESMAN, NETER, AND BECKER), 25

NEUMANN, ELIZABETH. (*See* SPAIN, STRAUSS, AND NEUMANN), 318

P

PACELLA, B. L. (*See* CHOBOT, DUNDY, AND PACELLA), 334

PERRY, DANIEL J., AND LEVAN, PAUL. Laboratory and clinical comparison of the "antihistaminic" effect of Hydryllin and four experimental compounds, 73

PINESS, GEORGE. (*See* WILLIAMS AND PINESS), 45

PRICE, WALTER C. An apparatus for aspiration of posterior pharyngeal secretions. Rubber-tip suction as an aid to obtaining postnasal mucoid material, 179

PRICKMAN, LOUIS E. (*See* CARRYER, KOELSCHE, PRICKMAN, MAYTUM, LAKE, AND WILLIAMS), 282

R

RANDOLPH, THERON G. Concepts of food allergy important in specific diagnosis, 471

— AND ROLLINS, JOHN P. The effect of cortisone on bronchial asthma, 288

RAWLING, FRANK F. A. (*See* FIGLEY AND RAWLING), 510, 545

REISS, FREDERICK, AND KERN, ARTHUR B. Clinical and experimental evaluation of Thephorin Ointment, 160

RISMAN, GEORGE, AND BOGER, WILLIAM P. Human skin sensitivity to penicillins G, BT, and O. Demonstration of cross-sensitization, 425

RODRIQUEZ, ARTHUR A. (*See* ROSTENBERG, LAST, AND RODRIQUEZ), 217

ROHDENBURG, GEORGE L. (*See* FARMER AND ROHDENBURG), 120

ROLLINS, JOHN P. (*See* RANDOLPH AND ROLLINS), 288

ROSE, B. (*See* HERBERT, DE VRIES, AND ROSE), 12

ROSSBACH, ELINOR A. (*See* KAILIN, ROSSBACH, AND WALZER), 225

ROSTENBERG, A., JR., LAST, JULES H., AND RODRIQUEZ, ARTHUR A. The effect of the development of an eczematous sensitization to a drug on the pharmacologic properties of that drug, 217

RUBITSKY, HYMAN, HERSCHFUS, J. AARON, LEVINSON, LEON, BRESNICK, ELLIOTT, AND SEGAL, MAURICE S. Evaluation of therapeutic substances employed for the relief of bronchospasm. VII. Combinations of diphenhydramine with ephedrine and aminophylline, 559

S

SAMTER, MAX. The effect of adrenocorticotrophic hormone (ACTH) on patients with allergic diseases—facts and speculations, 296

SANCHEZ-CUENCA, B. Penicilliosis and hypersensitiveness to penicillin, 176

SCHULMAN, PHILIP M. (*See* MCGAVACK, SHEARMAN, WEISSBERG, FUCHS, SCHULMAN, CHEVALLEY, DREKTER, AND BOYD), 353

SEEBOHM, PAUL M. (*See* SHERMAN AND SEEBOHM), 414

SEGAL, MAURICE S. (*See* RUBITSKY, HERSCHFUS, LEVINSON, BRESNICK, AND SEGAL), 559

SHEARMAN, ANN M. (*See* MCGAVACK, SHEARMAN, WEISSBERG, FUCHS, SCHULMAN, CHEVALLEY, DREKTER, AND BOYD), 353

SHERMAN, WILLIAM B. A case of coexisting insulin allergy and insulin resistance, 49

— AND COOKE, ROBERT A. Dermatitis following the use of Pyribenzamine and Antistine, 63

— AND SEEBOHM, PAUL M. Passive transfer of cold urticaria, 414

SHIMP, JAMES H. (*See* COULSON, SPIES, STEVENS, AND SHIMP), 34

SHURE, NORMAN. (*See* HARRIS AND SHURE), 208

SIMON, S. WILLIAM. Skin sensitivity to streptomycin. III., 400

SPAIN, W. C., STRAUSS, MARGARET B., AND NEUMANN, ELIZABETH. In vitro release of histamine by hypersensitive (allergic) serum in contrast to immune (treated) allergic serum in antigen and normal rabbit blood mixtures, 318

SPIES, JOSEPH R. (*See* COULSON, SPIES, AND STEVENS), 554

—. (*See* COULSON, SPIES, STEVENS, AND SHIMP), 34

STEVENS, HENRY. (*See* COULSON, SPIES, AND STEVENS), 554

—. (*See* COULSON, SPIES, STEVENS, AND SHIMP), 34

STRAUSS, MARGARET B. (*See* SPAIN, STRAUSS, AND NEUMANN), 318

STRITZLER, CONRAD. Studies on topical Thephorin therapy: index of sensitization and effectiveness as an antipruritic, 432

SULZBERGER, MARION B. Allergy: a dermatologist's reminiscences and speculations, 85

SWAEBLY, MARY ANN, CHRISTENSEN, CLYDE M., AND GRAHEK, THEODORE A. Tests of different media for the collection and identification of airborne saprophytic fungi, 404

SWINEFORD, OSCAR, JR. (*See* GUERRANT, MCCAUSLAND, AND SWINEFORD), 187

T

TREUTING, THEODORE. (*See* WOLF, HOLMES, TREUTING, GOODELL, AND WOLFF), 1

TUFT, HAROLD S. (*See* TUFT, TUFT, AND HECK), 181

TUFT, LOUIS, AND BLUMSTEIN, GEORGE I. (with the technical assistance of HECK, V. MURIEL.) Pollen tolerance nasal tests in hay fever. Experimental and clinical observations, 326

—, TUFT, HAROLD S., AND HECK, V. MURIEL. Atopic dermatitis. I. An experimental clinical study of the role of inhalant allergens, 181

W

WALDBOTT, G. L., KAUFMAN, J. M., AND MERKLE, K. J. Bronchiectasis in asthma, 339

WALZER, MATTHEW. (*See* CHAIT AND WALZER), 153

—. (*See* KAILIN, ROSSBACH, AND WALZER), 225

WEISSBERG, JONAS. (*See* MCGAVACK, SHEARMAN, WEISSBERG, FUCHS, SCHULMAN, CHEVALLEY, DREKTER, AND BOYD), 353

WHITE, ABRAHAM. Role of the adrenal cortex in immunity, 273

WHITE, W. A., JR., AND BAER, RUDOLF L. Failure to prevent experimental eczematous sensitization; observations on the "spontaneous" flare-up phenomenon, 344

WILLIAMS, HENRY L. (*See* CARRYER, KOELSCHE, PRICKMAN, MAYTUM, LAKE, AND WILLIAMS), 282

WILLIAMS, IDAMAE, AND PINESS, GEORGE. Efficiency of Phenylmercuric Acetate as a preservative in antigens, 45

WINKENWERDER, WALTER L. Symposium on food allergy: the internist's viewpoint, 487

WISEMAN, JOSEPH R., BROWN, BERNARD T., AND GANDIA, ANTONIO G. Asthma complicated by recurrent spontaneous pneumothorax, 199

WOLF, STEWART. (*See* GRAHAM, WOLF, AND WOLFF), 478

—, HOLMES, THOMAS H., TREUTING, THEODORE, GOODELL, HELEN, AND WOLFF, HAROLD G. An experimental approach to psychosomatic phenomena in rhinitis and asthma, 1

WOLFF, HAROLD G. (*See* GRAHAM, WOLF, AND WOLFF), 478

—. (*See* WOLF, HOLMES, TREUTING, GOODELL, AND WOLFF), 1

SUBJECT INDEX*

A

Abstracts, allergies, miscellaneous, *8, 23, 40, 54, 69, 86*
anaphylaxis, *10, 25, 42, 56, 71, 87*
asthma and hay fever, *1, 17, 33, 49, 65, 81*
dermatology, *4, 20, 36, 52, 67, 83*
miscellaneous, *14, 30, 47, 63, 78, 95*
otorhinology and ophthalmology, *7, 22, 38, 53, 69, 85*
pharmacology, physiology, and pathology, *10, 26, 43, 58, 73, 88*
Acetylcholine and potassium, sensibility of skeletal muscle to, effect of antihistaminic drugs on, *61* (Abst.)
reactions of isolated surviving coronary artery to, *62* (Abst.)
ACTH, administration of, effect of, on Loeffler's syndrome and tropical eosinophilia (Herbert et al.), 12
and cortisone, effect of, upon anaphylactoid reaction, *71* (Abst.)
effect of, in allergic diseases, preliminary observations on, *26* (Abst.)
on circulating antibody levels, *87* (Abst.)
on experimental cardiovascular lesions produced by anaphylactic hypersensitivity, *57* (Abst.)
on histamine intoxication and anaphylaxis in guinea pig (Friedlaender and Friedlaender), 303
on patients with allergic diseases (Samter), 296
electroencephalographic and neuropsychiatric changes in fifteen patients with, *74* (Abst.)
facts and speculations (Samter), 296
in asthma, preliminary report on, *65* (Abst.)
inhibition of Shwartzman phenomenon by, from the adenohypophysis, *61* (Abst.)
Adrenal cortex, role of, in immunity (White), 273
Adrenalin, hydrolysis of choline esters in presence of, *13* (Abst.)
Adrenaline, fluorescent development of, in paper chromatograms, *63* (Abst.)
Adrenergic agents for relief of bronchospasm, evaluation of, *1* (Abst.)
Adrenocortical extract, failure of, to modify immunity acquired by intact mice through use of pneumococcal vaccine, *15* (Abst.)
Adrenocorticotropic hormone, effect of, in allergic disease, preliminary observations on, *26* (Abst.)
on circulating antibody levels, *87* (Abst.)
on experimental cardiovascular lesions produced by anaphylactic hypersensitivity, *57* (Abst.)
on histamine intoxication and anaphylaxis in guinea pigs (Friedlaender and Friedlaender), 303
on patients with allergic diseases (Samter), 296
electroencephalographic and neuropsychiatric changes in fifteen patients with, *74* (Abst.)
in asthma, preliminary report on, *65* (Abst.)
inhibition of Shwartzman phenomenon by, from adenohypophysis, *61* (Abst.)
Aerosol delivery and stability during nebulization, procedure for determination of, *64* (Abst.)
Agranulocytosis after antihistaminic therapy, *78* (Abst.)
following Pyribenzamine, *32* (Abst.)
from tripelennamine hydrochloride, *78* (Abst.)
Air-borne saprophytic fungi, collection and identification of, tests of different media for (Swaebly et al.), 404
Airsickness, drugs in prevention of, effectiveness of various, *63* (Abst.)
Allergen, castor bean, identification of, in green coffee (Coulson et al.), 554
insect, the aphid (Gaillard), 386
wood dust as inhalant, *66* (Abst.)
Allergens, immunochemistry of. X. Anaphylactogenic properties of allergenic fractions from castor bean (Coulson et al.), 34
inhalant, in atopic dermatitis, importance of, *4* (Abst.)
role of, in atopic dermatitis, an experimental clinical study (Tuft et al.), 181
molds as (editorial), 465
nasal absorption of, in human beings, technique for studying (Chait and Walzer), 153
Allergic children, electroencephalographic patterns in, incidence of abnormal (Chobot et al.), 334

*Italic numbers indicate abstracts in section, Allergy Abstracts.

Allergic—Cont'd
dermatitis, fatal case of, with manifestations of combined collagen diseases, *75* (Abst.)
diseases, effect of ACTH in, preliminary observations on, *26* (Abst.)
on patients with (Samter), 296
suprarenal cortex in, investigations of the functions of, *59* (Abst.)
examination of bakers and millers, *51* (Abst.)
hypersensitivity, thyroid and adrenal hormones in, opposite actions of, *74* (Abst.)
meningitis and chronic erythema migrans Afzelii after bite by *Ixodes reduvius*, *55* (Abst.)
reactions to parenteral liver therapy and vitamin B_{12}, *70* (Abst.)
respiratory diseases, mold fungi in etiology of, *49*, *50* (Absts.)
rhinitis, iontophoresis of Pyribenzamine in, *69* (Abst.)
shock, acute, blood examination of hay fever patients during, *51* (Abst.)
specificity of pollens, *34* (Abst.)
Allergies, miscellaneous, *8*, *23*, *49*, *54*, *69*, *86* (Absts.)
Allergy: a dermatologist's reminiscences and speculations (Sulzberger), 85
and migraine, *24* (Abst.)
as cause of nuchal myalgia and associated headache, *39* (Abst.)
bacterial, psoriasis, *86* (Abst.)
sinusitis due to, *54* (Abst.)
complement fixation studies in (Cavelti), 532
drug, in canine family, *25* (Abst.)
food (editorial), 563
acute vs. chronic (Mitchell), 514
concepts of, important in specific diagnosis (Randolph), 471
provocative diets in recognition of, *42* (Abst.)
symposium on, American Academy of Allergy, sixth annual meeting, Los Angeles, Calif., March 6-8, 1950, 471
the internist's viewpoint (Winkenwerder), 487
for corn and its derivatives, diagnosis of, experiments with a masked ingestion test for (Loveless), 500
in asthma, other factors besides, *35* (Abst.)
induction of, by inhalation of allergens, experiments in, *34* (Abst.)
insulin, and insulin resistance, case of coexisting (Sherman), 45
generalized, *54* (Abst.)
milk: survey of its incidence; experiments with a masked ingestion test (Loveless), 489
of eye associated with migraine headache, *24* (Abst.)
of infection, studies in, *30* (Abst.)
Allergy—Cont'd
quinidine, *92* (Abst.)
respiratory, due to fungi, *65* (Abst.)
in children, treatment of, by oral administration of dust and pollen extracts (Black and Holman), 148
role of, in epidemiology of common cold, *85* (Abst.)
in pathogenesis of rheumatic fever, *27* (Abst.)
sludged blood in, *61* (Abst.)
tests, sudden death due to (Harris and Shure), 208
tissue sensitivity, changes in, with varying life situations and emotions and their relevance to (Graham et al.), 478
to human dander, observations on, *4* (Abst.)
to molds in Sweden, botanical and clinical study, *3* (Abst.)
to Pyribenzamine and Antistine (Sherman and Cooke), 63
Alum precipitated pyridine, poison ivy treated with, summary of 100 cases (Gaillard), 55
Amalgam dental fillings, contact dermatitis due to mercury of, *20* (Abst.)
Amebiasis, urticaria and angio-edema in association with, *83* (Abst.)
American Academy of Allergy, announcements, 83, 467
report of the Pollen Survey Committee of, for season of 1949 (Durham), 442
report of sixth annual meeting, 252
report of Subcommittee on Mold Survey of the Research Council, for season of 1949 (Harris), 455
symposium on food allergy given before the sixth annual meeting, Los Angeles, Calif., March 6-8, 1950, 471
transactions of fifth annual meeting, Atlantic City, N. J., December 6-8, 1949, 1
sixth annual meeting, Los Angeles, Calif., March 6-8, 1950, 181, 273, 373, 471
Aminophylline, administration of, *77* (Abst.)
effect of, on prothrombin time of normal human plasma, *93* (Abst.)
in relief of bronchospasm, evaluation of, *26* (Abst.)
Ammoniated mercury, idiosyncrasy to; treatment with BAL, *68* (Abst.)
Anaphylactic and trypsin shock, chromatographic demonstration of histamine release in, *43* (Abst.)
hypersensitivity, experimental cardiovascular lesions produced by, effect of ACTH upon, *57* (Abst.)
reaction following heparin injection, *69* (Abst.)
to intravenous procaine, *55* (Abst.)

Anaphylactic—Cont'd
shock, effect of flavonoid (vitamin P-like) substances on (Clark and MacKay), 133
role of adrenal glands in, guinea pig, *87* (Abst.)
Anaphylactogenic properties of allergenic fractions from castor bean (Coulson et al.), 34
Anaphylactoid reaction, effect of ACTH and cortisone on, *71* (Abst.)
to sulfobromophthalein sodium, *70* (Abst.)
shock, blood histamine in, *87* (Abst.)
due to penicillin, *42* (Abst.)
Anaphylaxis, *10, 25, 42, 56, 71, 87* (Absts.)
in guinea pig, effect of ACTH on histamine intoxication and (Friedlaender and Friedlaender), 303
peripheral vascular reactions in mouse, *71* (Abst.)
reversed, in guinea pigs, effect of Pyribenzamine, Neohetramine, and rutin on (Arbesman et al.), 25
Anemia following antihistaminic drugs, *78* (Abst.)
Angioneurotic edema and rash due to aureomycin, *83* (Abst.)
Announcements, American Academy of Allergy, 467
Canadian Society for Study of Allergy, 468
clinical training in allergy, Northwestern University Medical School, 566
mold and pollen identification, three-day course in, 566
Second International Congress on Asthma, 468
Anoxemia, reduction in number of circulating eosinophils following induced, *61* (Abst.)
Anoxemic patients, chronically, mental changes occurring in, during oxygen therapy, *81* (Abst.)
Ant bites, unusual reactions to, *9* (Abst.)
Antabuse, fixed drug eruption from, *68* (Abst.)
Antibiotic, bacitracin, a new, use of, in aerosol form, *88* (Abst.)
Antibodies, physiologic and immune, titration of, with washed and unwashed erythrocytes, *32* (Abst.)
production of, toxemia as stimulation factor in, *10* (Abst.)
zone of localization of, *48, 95* (Absts.)
Antibody production by lymphatic tissue, biologic and technical factors in demonstration of, *58* (Abst.)
in guinea pig, ascorbic acid and, *96* (Abst.)
relation of nutritional deficiency in man to, *94* (Abst.)
release, relation of adrenal cortical steroids to, *93* (Abst.)
Antigen-antibody reactions as demonstrated by serum-agar technic, *96* (Abst.)
Antigen—Cont'd
Ascaris lumbricoides, sensitization to, factors influencing reagin formation in experimental human. IV. The influence of a previous sensitization to rate of sensitization (Kailin et al.), 225
in tissue cells, localization of, *79* (Abst.)
ragweed, effect of slowly absorbing, on neutralizing antibody titer (Malkiel and Feinberg), 525
tobacco, cutaneous reactions to, in allergic and nonallergic children, *55* (Abst.)
Antigenicity of banana, raw and dehydrated, studies on (Fries and Glazer), 169
of collagen, *42* (Abst.)
Antigens, Phenylmercuric Acetate as a preservative in, efficiency of (Williams and Piness), 45
Antihistamine agent, effect of, on various whealing phenomena, *11* (Abst.)
drugs and rutin, tuberculin type reaction by, inhibition of, *41* (Abst.)
failure of, to inhibit hyaluronidase in vitro, *16* (Abst.)
Pyribenzamine and Antistine, dermatitis following use of (Sherman and Cooke), 63
Neohetramine, and rutin, effect of, on reversed anaphylaxis in guinea pigs (Arbesman et al.), 25
effect of, on localization of trypan blue in xylene-treated areas of skin, *12* (Abst.)
medication, effect of, on tuberculin reaction in children, *47* (Abst.)
ointments for skin protection in radiation therapy, *21* (Abst.)
therapy in experimental shock, *92* (Abst.)
in thrombophlebitis migrans, *16* (Abst.)
Antihistamines as antidote against histamine-like effect of curare preparations, *13* (Abst.)
in bronchial asthma, *9* (Abst.)
Antihistaminic activity of orally administered compounds, duration of, experimental determination in human subjects, *13* (Abst.)
agents, their metabolism by means of quantitative analytical methods, studies of, *91* (Abst.)
drug, effect of treatment with, on blood pressure and urine in pregnant women, *93* (Abst.)
Phenergan, failure of, to protect against acute pulmonary edema, *90* (Abst.)
treatment of common cold with, study of, *60* (Abst.)
drugs, anemia following use of, *78* (Abst.)
comparative activity in man as measured by histamine iontophoresis, *60* (Abst.)
effect of, on sensibility of skeletal muscle to acetylcholine and potassium, *61* (Abst.)

Antihistaminic drugs—Cont'd
failure of, to influence the local vascular changes in experimental burns, *91* (Abst.)
for colds, evaluation, *63* (Abst.)
therapy, agranulocytosis after, *78* (Abst.)
Antihistaminics, newer: III. Some pharmacologic and therapeutic effects of β-(p-methylbenzhydryloxy)-ethyldimethylamine hydrochloride, a derivative of diphenhydramine hydrochloride (McGavack et al.), 353
their clinical application (book review), 565
Anti-rat-liver serum, effect of, in rats, *88* (Abst.)
Antisera, production of, in rabbits using calcium alginate as an antigen depot, *64* (Abst.)
Antistine, dermatitis following use of (Sherman and Cooke), 63
sensitization to, *53* (Abst.)
Aphid—an insect allergen (Gaillard), 386
Arterenol, pulmonary edema from, *2* (Abst.)
Arthritis, rheumatoid, serological reactions in, *63* (Abst.)
Arthus phenomenon, quantitative study of, induced passively in the guinea pig, *56* (Abst.)
Ascaris lumbricoides antigen, sensitization to, factors influencing reagin formation in experimental human. IV. The influence of a previous sensitization on rate of sensitization (Kailin et al.), 225
tissue and fluids, toxic and allergic manifestations caused by, *57* (Abst.)
Ascorbic acid and production of antibody in guinea pig, *96* (Abst.)
Aspiration of posterior pharyngeal secretions, apparatus for (Price), 179
Asthma, ACTH in, preliminary report on, *65* (Abst.)
allergy in, other factors besides, *35* (Abst.)
and emphysema, cardiorespiratory function in relation to, allergist's viewpoint (Baldwin), 349
and hay fever, *1, 17, 33, 49, 65, 81* (Absts.)
bronchial, and hay fever, effect of cortisone on, in subjects sensitive to ragweed pollen (Carryer et al.), 282
antihistamines in, *9* (Abst.)
caused by inhalation of wood dust, *18* (Abst.)
by wood, *66* (Abst.)
death in case of, treated successively with intravenous procaine and Sodium Amytal, *19* (Abst.)
effect of cortisone on (Randolph and Rollins), 288
histamine and methacholine in, effect of Dihydroergocornine on pulmonary response to, *17* (Abst.)
in general practice, incidence of, *67* (Abst.)
Asthma, bronchial—Cont'd
mediastinal emphysema occurring during acute paroxysm of, *3* (Abst.)
parenteral and aerosol administration of antihistaminic agents in treatment of severe, *18* (Abst.)
ventilatory tests in (Gaensler), 232
bronchiectasis in (Waldbott et al.), 339
complicated by recurrent spontaneous pneumothorax (Wiseman et al.), 199
disseminated focal necrosis with eosinophilia and arteritis in case of, *82* (Abst.)
in children, *34* (Abst.)
physiotherapy of, *19* (Abst.)
psychosomatic phenomena in, experimental approach to (Wolf et al.), 1
respiratory exercises in, *19* (Abst.)
specific desensitization in, control examination of specificity of, *19* (Abst.)
with sinus disease; comparison of radical sinus surgery and conservative treatment (Guerrant et al.), 187
Atmosphere, mold spores in, a census of, *35* (Abst.)
Atmospheric pollen studies, preliminary report, *66* (Abst.)
Atopic dermatitis, fungus studies in, *38* (Abst.)
I. An experimental clinical study of the role of inhalant allergens (Tuft et al.), 181
inhalant allergens in, importance of, *4* (Abst.)
eczema, study of, *4* (Abst.)
Aureomycin, angioneurotic edema and rash due to, *83* (Abst.)
eczema vaccinatum treated with; rapid recovery, *15* (Abst.)
Kaposi's varicelliform eruption treated with, report of case, and observations regarding course of underlying skin disease (Bookman), 68
sensitivity reactions to, *68* (Abst.)
Autogenous antigens, local organ hypersensitivity to (Jahiel and Jahiel), 102
Azoproteins, blue antigenic, distribution and storage of, in tissue of mice, *14* (Abst.)

B

Bacitracin, a new antibiotic, use of, in aerosol form, *88* (Abst.)
Bacterial flora of pharynx and nasopharynx, comparison of, *23* (Abst.)
Bakers, allergic examination of, *51* (Abst.)
BAL, treatment of ammoniated mercury sensitivity with, *68* (Abst.)
B-aminoethyl hetero-cyclic nitrogen compounds, histamine activity of some, *92* (Abst.)
Banana, raw and dehydrated, antigenicity of (Fries and Glazer), 169

BCG test, the diagnostic, *16* (Abst.)
tuberculin as testing material, *31* (Abst.)
vaccination, responses of skin to, in various categories of tuberculin sensitivity, *30* (Abst.)
Bee, sting of, histology of lesions caused by, *70* (Abst.)
Benadryl, effect of, on Herxheimer reaction after use of penicillin, *47* (Abst.)
poisoning, accidental, *29* (Abst.)
Benzoin, compound tincture of, contact-type dermatitis due to, investigation of, *37* (Abst.)
Bis-beta-chloroethyl amine, inhibitory effect of, on lesions of experimental serum hypersensitiveness, *45* (Abst.)
Bite by *Ixodes reduvius*, allergic meningitis and chronic erythema migrans Afzelii after, *55* (Abst.)
Bites, ant, unusual reactions to, *9* (Abst.)
Bleeding time, effect of flavonoid (vitamin P-like) substances on (Clark and MacKay), 133
Book reviews, 271, 470, 565
Bronchial asthma and hay fever, effect of cortisone on, in subjects sensitive to ragweed pollen (Carryer et al.), 282
antihistamines in, *9* (Abst.)
caused by inhalation of wood dust, *18* (Abst.)
by wood, *66* (Abst.)
death in case of, treated successively with intravenous procaine and Sodium Amytal, *19* (Abst.)
effect of cortisone on (Randolph and Rollins), 288
histamine and methacholine in, effect of Dihydroergocornine on pulmonary response to, *17* (Abst.)
in general practice, incidence of, *67* (Abst.)
mediastinal emphysema occurring during acute paroxysm of, *3* (Abst.)
parenteral and aerosol administration of antihistaminic agents in treatment of severe, *18* (Abst.)
ventilatory tests in (Gaensler), 232
Bronchiectasis, curative treatment by pulmonary resection, *3* (Abst.)
in asthma (Waldbott et al.), 339
in childhood, clinical survey, *17* (Abst.)
study of segmental distribution of pathologic lesions, *51* (Abst.)
Bronchospasm, relief of, aminophylline in, evaluation of, *26* (Abst.)
historical development and methods, *2* (Abst.)
therapeutic substances employed for, evaluation of, *1, 2* (Absts.)
VII. Combinations of diphenhydramine with ephedrine and aminophylline (Rubitsky et al.), 559
Bullae in pemphigus, production of, with hyaluronidase, *36* (Abst.)
Burlap bags, used, castor bean an industrial hazard as a contaminant of (Figley and Rawling), 545
Burn shock, effect of tripelennamine hydrochloride in, *47* (Abst.)
Burns, experimental, failure of antihistaminic drugs to influence the local vascular changes in, *91* (Abst.)

C

Canadian Society for Study of Allergy, announcement of, 468
Capillary permeability to dye, histamine-enhanced, effect of flavonoid (vitamin P-like) substances on (Clark and MacKay), 133
Cardiac lesions resembling rheumatic fever, induction of, in rabbits following repeated skin injections with group A streptococci, *76* (Abst.)
Cardiorespiratory function in relation to asthma and emphysema, allergist's viewpoint (Baldwin), 349
Cardiovascular lesions, experimental, produced by anaphylactic hypersensitivity, effect of ACTH upon, *57* (Abst.)
histamine induced (Farmer and Rohdenburg), 120
Castor bean allergen, identification of, in green coffee (Coulson et al.), 554
allergenic fractions from, anaphylactogenic properties of (Coulson et al.), 34
an industrial hazard as a contaminant of green coffee dust and used burlap bags (Figley and Rawling), 545
Cigarette paper dermatitis, *37* (Abst.)
Ciliary activity, study of, in respiratory tract of animals, *7* (Abst.)
Cinnamon, contact dermatitis due to, *84* (Abst.)
Circulating antibody, formation of, in adult male albino rat, effect of splenectomy on, *88* (Abst.)
Coffee dust, green, castor bean an industrial hazard as a contaminant of (Figley and Rawling), 545
green, castor bean allergen in, identification of (Coulson et al.), 554
Cold, common, antihistaminic agents and ascorbic acid in early treatment of, *69* (Abst.)
epidemiology of, role of allergy in, *85* (Abst.)
infections of, active immunization against secondary bacterial, *38, 39* (Absts.)
research on, *8* (Abst.)
studies on, *8* (Abst.)
treatment of, with antihistaminic drug, study on, *60* (Abst.)
virus vaccine immunization against, *31* (Abst.)

Cold—Cont'd
urticaria, passive transfer of (Sherman and Seebohm), 414
Colds, antihistaminic drugs for, evaluation of, *63* (Abst.)
Collagen, antigenicity of, *42* (Abst.)
Complement fixation studies in allergy (Cavelti), 532
Contact dermatitis due to cinnamon, *84* (Abst.)
due to mercury of amalgam dental fillings, *20* (Abst.)
due to phenolphthalein, *7* (Abst.)
due to procaine, *6* (Abst.)
Cor pulmonale, chronic, neurological effects of oxygen in, *90* (Abst.)
Corn and its derivatives, allergy for, diagnosis of, experiments with a masked ingestion test for (Loveless), 500
sensitivity, clinical experience in (Figley and Rawling), 510
diagnostic tests in, clinical experience with objective (Cazort), 512
Coronary arteries, polyarteritis nodosa of, *44* (Abst.)
artery, reactions of isolated surviving, to epinephrine, acetylcholine and histamine, *62* (Abst.)
Correspondence, 80
Cortisone and ACTH, effect of, upon anaphylactoid reaction, *71* (Abst.)
and adrenocorticotropin, treatment of disseminated lupus erythematosus with, *73* (Abst.)
effect of, on bronchial asthma (Randolph and Rollins), 288
and hay fever in subjects sensitive to ragweed pollen (Carryer et al.), 282
on release of histamine during in vitro hemolytic reactions in rabbit blood (Carryer and Code), 310
Curare preparations, histamine-like effect of, antihistamines as antidote against, *13* (Abst.)
Cutaneous hypersensitivity to tuberculin in man, cellular transfer of, *54* (Abst.)
lesions occurring in course of streptomycin therapy, *36* (Abst.)
reactions to insulin, mechanism of, *55* (Abst.)
to tobacco antigen in allergic and nonallergic children, *55* (Abst.)

D

Dander, human, allergy to, observations on, *4* (Abst.)
DDT, exfoliative dermatitis from contact with, *6* (Abst.)
Death due to allergy tests (Harris and Shure), 208
Dermatitis, allergic, fatal case of, with manifestations of combined collagen diseases, *75* (Abst.)
Dermatitis—Cont'd
atopic, fungus studies in, *38* (Abst.)
I. An experimental clinical study of the role of inhalant allergens (Tuft et al.), 181
inhalant allergens in, importance of, *4* (Abst.)
caused by electrode jelly, *21* (Abst.)
cigarette paper, *37* (Abst.)
contact, due to cinnamon, *84* (Abst.)
due to compound tincture of benzoin, investigation of, *37* (Abst.)
due to mercury of amalgam dental fillings, *20* (Abst.)
due to phenolphthalein, *7* (Abst.)
due to procaine, *6* (Abst.)
eczematous, specific sensitivity to foods in, *22* (Abst.)
exfoliative, and hepatitis due to phenobarbital, *84* (Abst.)
due to penicillin and streptomycin, *52* (Abst.)
from contact with DDT, *6* (Abst.)
following use of Pyribenzamine and Antistine (Sherman and Cooke), 63
lipstick, *68* (Abst.)
medicamentosa due to undecylenic acid, *53* (Abst.)
ragweed, therapy by oral route, *6* (Abst.)
Rhus toxicodendron, prophylaxis of, *83* (Abst.)
Dermatographic prurigo, *83* (Abst.)
Dermatology, *4*, *20*, *36*, *52*, *67*, *83* (Absts.)
McClure-Aldrich test in, with special reference to the dermatoses, *52* (Abst.)
Dibenamine, chemical basis for adrenergic blocking activity in compounds related to, *89* (Abst.)
Dihydroergocornine, effect of, on pulmonary response to histamine and methacholine in bronchial asthma, *17* (Abst.)
Diphenhydramine, combinations of, with ephedrine and aminophylline in relief of bronchospasm (Rubitsky et al.), 559
hydrochloride, effect of, on Herxheimer reaction after use of penicillin, *47* (Abst.)
Diseases of connective tissue, serum proteins in, *52* (Abst.)
Drug allergy in canine family, *25* (Abst.)
eczematous sensitization to a, effect of development of, on the pharmacologic properties of that drug (Rostenberg et al.), 217
eruption from tetraethylthiuram disulfide, fixed, *68* (Abst.)
Drugs, effect of various, on the wheal reaction, study of (Mosko and Marshall), 242
in prevention of airsickness, effectiveness of various, *63* (Abst.)
used in local anesthetics, toxicity of, *16* (Abst.)

d-Tubocurarine, liberation of heparin and histamine by, *46* (Abst.)
Dust, wood, as inhalant allergen, *66* (Abst.)
bronchial asthma caused by inhalation of, *18* (Abst.)

E

Eczema, atopic, study of, *4* (Abst.)
scales, cutaneous reactions to, *4* (Abst.)
vaccinatum treated with aureomycin: rapid recovery, *15* (Abst.)
Eczematous dermatitis, specific sensitivity to foods in, *22* (Abst.)
sensitization, experimental, failure to prevent (White and Baer), 344
to drug, effect of development of, on the pharmacologic properties of that drug (Rostenberg et al.), 217
Edematous reactions to trichophytin, immediate wheal and 24-48 hour tuberculin type, *5* (Abst.)
Editorial, Dr. Harry L. Alexander retires as editor, 371
food allergy, 563
molds as allergens, 465
Egg white, chemical fractions of, skin test reactions to, clinical significance (Miller and Campbell), 522
Electrode jelly, dermatitis caused by, *21* (Abst.)
Electroencephalographic patterns in allergic children, incidence of abnormal (Chobot et al.), 334
Electrophoresis-convection method for reagic serum fractions (Campbell et al.), 519
Emphysema and asthma, cardiorespiratory function in relation to, allergist's viewpoint (Baldwin), 349
Eosinopenia due to glucose administration, *60* (Abst.)
Eosinophilia, transitory infiltrates in the lungs with, *35* (Abst.)
Eosinophilic granuloma of jejunum, *76* (Abst.)
Eosinophils of mice, effects of stress, adrenal and adrenocorticotrophic hormones on the circulating, *28* (Abst.)
reduction in number of circulating, following induced anoxemia, *61* (Abst.)
Epidemiology of common cold, role of allergy in, *85* (Abst.)
Epinephrine, acute lethal effect of, in rats, mechanism of, *59* (Abst.)
cutaneous action of, effect of adrenergic blocking agents on, *45* (Abst.)
fastness, an approach to problem of, *82* (Abst.)
intradermal, local sweating in man induced by, *10* (Abst.)
iontropic action of, on heart muscle, *90* (Abst.)
Epinephrine—Cont'd
large doses of, physiologic effects of, studies on, *94* (Abst.)
reactions of isolated surviving coronary artery to, *62* (Abst.)
stress, resistance to, in dog, *91* (Abst.)
Ergotamine, intravenous, acute coronary insufficiency pattern following, *92* (Abst.)
Eruption from tetraethylthiuram disulfide, fixed drug, *68* (Abst.)
Erythema nodosum, etiology, *16* (Abst.)
Exfoliative dermatitis and hepatitis due to phenobarbital, *84* (Abst.)
due to contact with DDT, *6* (Abst.)
due to penicillin and streptomycin, *52* (Abst.)
Eye, allergy of, associated with migraine headache, *24* (Abst.)

F

Favism, report of case in child, *25* (Abst.)
Fibrocystic disease of pancreas, pathogenesis of, *29* (Abst.)
therapy and prognosis of, *31* (Abst.)
Flavonoid (vitamin P-like) substances, effect of, on histamine toxicity, anaphylactic shock, histamine-enhanced capillary permeability to dye, and bleeding time (Clark and MacKay), 133
Flavonoids, toxicity of (Clark and MacKay), 133
Flora of nose and nasopharynx in adults, bacteriologic and classical interpretation of, *85* (Abst.)
Folic acid, hypersensitivity to, *40* (Abst.)
Food allergy (editorial), 563
acute vs. chronic (Mitchell), 514
concepts of, important in specific diagnosis (Randolph), 471
provocative diets in recognition of, *42* (Abst.)
symposium on, American Academy of Allergy, sixth annual meeting, Los Angeles, Calif., March 6-8, 1950, 471
the internist's viewpoint (Winkenwerder), 487
Foods, sensitivity to, specific, as factor in eczematous dermatitis, *22* (Abst.)
Footwear, primary irritants and sensitizers, used in fabrication of, *37* (Abst.)
Fractionation, serum, electrophoresis-convection method for (Campbell et al.), 519
Fumes from range oil, persistent cough and bronchospasm due to, *66* (Abst.)
Fungi, air-borne saprophytic, collection and identification of, tests of different media for (Swaebly et al.), 404
respiratory allergy due to, *65* (Abst.)

Fungus studies in atopic dermatitis, *38* (Abst.)
Furacin, sensitivity to, *67* (Abst.)

G

Gamma globulin in relation to infections of respiratory tract, *23* (Abst.)
Giardia lamblia, chronic urticaria due to, *20* (Abst.)
Glucose administration, eosinopenia due to, *60* (Abst.)

H

Hay fever and asthma, *1, 17, 33, 49, 65, 81* (Absts.)
bronchial, effect of cortisone on, in subjects sensitive to ragweed pollen (Carryer et al.), 282
patients, blood examination of, during acute allergic shock, *51* (Abst.)
pollen tolerance nasal tests in, experimental and clinical observations (Tuft and Blumstein), 326
Headache, experimental studies on, *53* (Abst.)
migraine, allergy of eye associated with, *24* (Abst.)
vasodilating, methyl-iso-octenylamine in treatment of, evaluation of, *24* (Abst.)
Heart muscle, inotropic action of epinephrine on, *90* (Abst.)
Hematuria, idiopathic purpura associated with, *41* (Abst.)
Heparin, anaphylactic reaction following injection of, *69* (Abst.)
and histamine, liberation of, by d-tubocurarine, *46* (Abst.)
Herpes simplex infections, serological diagnosis of, *96* (Abst.)
Herxheimer reaction after use of penicillin, effect of Benadryl on, *47* (Abst.)
Hesperidin chalcone sodium, treatment of allergic and vasomotor rhinitis with, *39* (Abst.)
Histamine, administration of, during pregnancy, *12* (Abst.)
and uveal infiltration, *23* (Abst.)
antagonists, action of, on histamine wheal and the eczema test, *84* (Abst.)
effect of cortisone upon the release of, in vitro hemolitic reactions in rabbit blood (Carryer and Code), 310
of tripelennamine hydrochloride on release of, during in vitro hemolytic reaction in rabbit blood (Carryer and Code), 314
excretion in urine, *76* (Abst.)
in vitro release of, by hypersensitive (allergic) serum in contrast to immune (treated) allergic serum in antigen and normal rabbit blood mixtures (Spain et al.), 318
Histamine, in vitro release of—Cont'd
from blood cells of sensitized rabbits, *25* (Abst.)
induced cardiovascular lesions (Farmer and Rohdenburg), 120
intoxication and anaphylaxis in guinea pig, effect of ACTH on (Friedlaender and Friedlaender), 303
iontophoresis, comparative activity of antihistaminic drugs in man, as measured by, *60* (Abst.)
mechanism of, *27* (Abst.)
metabolism in pregnancy, *11, 62* (Absts.)
nonconvulsive biochemotherapy with, *48* (Abst.)
reactions of isolated surviving coronary artery to, *62* (Abst.)
release of, during hemolytic reactions in blood of rabbits, *62* (Abst.)
toxicity, effect of flavonoid (vitamin P-like) substances on (Clark and MacKay), 133
Hormodendrum resinae, spores of, intramural dissemination of (Christensen), 409
Horse serum, lesions of hypersensitivity induced in rabbits by massive injections of, *58* (Abst.)
Hyaluronidase in albino rat, action of tripelennamine on, *28* (Abst.)
in vivo, inhibition of, by adrenal cortical activation, *89* (Abst.)
production of bullae in pemphigus with, *36* (Abst.)
Hydryllin, antihistaminic effect of, laboratory and clinical comparison of, and four experimental compounds (Perry and LeVan), 73
Hypersensitiveness, effect of x-ray radiation on (Criep et al.), 373
serum, inhibitory effect of nitrogen mustard on lesions of experimental, *45* (Abst.)
to penicillin, penicilliosis and (Sanchez-Cuenca), 176
Hypersensitivity, allergic, thyroid and adrenal hormones in opposite actions of, *74* (Abst.)
anaphylactic, experimental cardiovascular lesions produced by, effect of ACTH upon, *57* (Abst.)
delayed, role of "wax" of tubercle bacillus in establishing, *72* (Abst.)
lesions of, produced in rabbits by horse serum, *58* (Abst.)
local organ, to autogenous antigens (Jahiel and Jahiel), 102
procaine, treatment with neostigmine, *88* (Abst.)
reactions, effect of sodium salicylate upon, *87* (Abst.)
to folic acid, *40* (Abst.)
to Pitressin, *23* (Abst.)
to tuberculin in man, cellular transfer of cutaneous, *54* (Abst.)
vascular diseases due to, *45* (Abst.)

I

Idiopathic purpura associated with hematuria, *41* (Abst.)
Immunity, role of adrenal cortex in (White), 273
Immunochemistry of allergens. X. Anaphylactogenic properties of allergenic fractions from castor bean (Coulson et al.), 34
Infection, allergy of, *30* (Abst.)
Ingestion test for diagnosis of allergy for corn and its derivatives, experiments with a masked (Loveless), 500
in milk allergy, experiments with a masked (Loveless), 489
Inhalant allergen, wood dust as, *66* (Abst.)
allergens in atopic dermatitis, importance of, *4* (Abst.)
role of, in atopic dermatitis, an experimental clinical study (Tuft et al.), 181
Inhalation of allergens, induction of allergy by, experiments in, *34* (Abst.)
Inhalators, oral and nasal, contact systemic penicillin reactions associated with, *4* (Abst.)
Insect allergen, aphid (Gaillard), 386
Insulin allergy and insulin resistance, a case of coexisting (Sherman), 49
generalized, *54* (Abst.)
cutaneous reactions to, mechanism of, *55* (Abst.)
International Congress on Asthma, Second, announcement of, 468
Internist's viewpoint on food allergy, (Winkenwerder), 487
Intramural dissemination of spores of *Hormodendrum resinae* (Christensen), 409
Iodine, thrombotic thrombopenic purpura caused by, *48* (Abst.)
Iontophoresis of Pyribenzamine in allergic rhinitis, *69* (Abst.)
Irritants and sensitizers, primary, used in fabrication of footwear, *37* (Abst.)
Isoallergic encephalomyelitis produced in guinea pigs by intramuscular and intraperitoneal injection of antigen, *73* (Abst.)
Isuprel, bronchodilator activity of some analogues of, *47* (Abst.)

K

Kaposi's varicelliform eruption treated with aureomycin, report of case of, and observations regarding course of underlying skin disease (Bookman), 68

L

Leucocyte picture of rat; relation of adrenal and spleen, *47* (Abst.)
Leucocytes, in vitro lysis of, by tuberculoprotein, nature of plasma factor responsible for, *40* (Abst.)
Lipstick dermatitis, *68* (Abst.)
Liver circulation, studies on; hepatic venous tree, active constriction of, in anaphylactic shock, *72* (Abst.)
Loeffler's endocarditis parietalis fibroplastica, early stage of, with eosinophilia, *82* (Abst.)
syndrome, effect of administration of ACTH in (Herbert et al.), 12
Lupus erythematosus, treatment of disseminated, with cortisone and adrenocorticotropin, *73* (Abst.)

M

McClure-Aldrich test in dermatology, with special reference to the dermatoses, *52* (Abst.)
Media tests for collection and identification of air-borne saprophytic fungi (Swaebly et al.), 404
Mercupurin, urticaria due to, *20* (Abst.)
Mercurial diuretics, sensitivity to, *20* (Abst.)
Metabolism, histamine, in pregnancy, *11*, *62* (Absts.)
Methyl-iso-octenylamine in treatment of vasodilating headaches, evaluation of, *24* (Abst.)
Migraine and allergy, *24* (Abst.)
headache, allergy of eye associated with, *24* (Abst.)
Milk allergy: survey of its incidence; experiments with a masked ingestion test (Loveless), 489
Millers, allergic examination of, *51* (Abst.)
Mold fungi in etiology of respiratory allergic diseases, *49*, *50* (Absts.)
spores in atmosphere, a census of, *35* (Abst.)
Mold Survey, report of Subcommittee on, of the Research Council, American Academy of Allergy, for the season of 1949 (Harris), 455
Molds as allergens (editorial), 465
in Sweden, allergy to, botanical and clinical study, *3* (Abst.)
Mucous membrane sensitization, studies in, *38* (Abst.)
Mumps virus vaccine, chick embryo propagated, immunologic response of children to injection of, *95* (Abst.)
Myocardial infarction following administration of tetanus antitoxin, *29* (Abst.)

N

Nasal absorption of allergens in human beings, technique for studying (Chait and Walzer), 148

Nasal—Cont'd
tests in hay fever, pollen tolerance, experimental and clinical observations (Tuft and Blumstein), 326
turbinates, *22* (Abst.)
N-dimethylamino-methyl-ethyl-dibenzoparathiazine, vascular effects of, *29* (Abst.)
Neohetramine, Pyribenzamine, and rutin, effect of, on reversed anaphylaxis in guinea pigs (Arbesman et al.), 25
Neostigmine, treatment of procaine "hypersensitivity" with, *88* (Abst.)
N-isopropylarterenol, bronchodilator activity of some analogues of, *47* (Abst.)
Nitrogen compounds, histamine activity of some, *92* (Abst.)
Nitrogen mustard, inhibitory effect of, on lesions of experimental serum hypersensitiveness, *45* (Abst.)
Nuchal myalgia and associated headache, allergy as a cause of, *39* (Abst.)

O

Oak and ragweed pollens, air-borne, at Columbus Ohio, volumetric and gravity slide tests for, *49* (Abst.)
Oil, fumes from range, persistent cough and bronchospasm due to, *66* (Abst.)
Otorhinology and ophthalmology, *7, 22, 38, 53, 69, 85* (Absts.)
Oxygen, neurological effects of, in chronic cor pulmonale, *90* (Abst.)

P

Panarteritis, disseminated necrotizing, *77* (Abst.)
Pancreas, fibrocystic disease of, pathogenesis of, *29* (Abst.)
therapy and prognosis of, *31* (Abst.)
Paper chromatograms, adrenaline in, fluorescent development of, *63* (Abst.)
Para-aminosalicylic acid, sensitization to, *41* (Abst.)
Paradione and Tridione in treatment of epilepsy, comparison of, *67* (Abst.)
Paraphenylenediamine-hypersensitive subjects, effects of feeding certified food azodyes in, *21* (Abst.)
Patch test, action of histamine antagonists on histamine wheal and, *84* (Abst.)
evaluation of, based on experimental findings, *6* (Abst.)
reactions, eczematous and toxic, cellular content of exudates from, *5* (Abst.)
tuberculin, pseudoreactions to, *15* (Abst.)
tests versus usage tests, *20* (Abst.)
Penicillin, anaphylactoid shock due to, *42* (Abst.)
exfoliative dermatitis due to, *52* (Abst.)
Penicillin—Cont'd
Herxheimer reaction after use of, effect of Benadryl on, *47* (Abst.)
hypersensitiveness to, penicilliosis and (Sanchez-Cuenca), 176
in oil and wax, pulmonary embolism following injection of, *48* (Abst.)
reaction to, an unusual, *71* (Abst.)
reactions, contact systemic, associated with oral and nasal inhalators, *4* (Abst.)
Shwartzman phenomenon with, *9* (Abst.)
tooth powder containing, effect of, on mucous membrane, *38* (Abst.)
Penicillins G, BT, and O, skin sensitivity to; demonstration of cross-sensitization (Risman and Boger), 425
Penicilliosis and hypersensitiveness to penicillin (Sanchez-Cuenca), 176
Periarteritis nodosa—asthma bronchiale—iododerina tuberosum, *76* (Abst.)
Pharmacology, physiology, and pathology, *10, 26, 43, 58, 73, 88* (Absts.)
Pharyngeal secretions, posterior, apparatus for aspiration of (Price), 179
Pharynx and nasopharynx, bacterial flora of, comparison of, *23* (Abst.)
Phenergan, failure of, to protect against acute pulmonary edema, *90* (Abst.)
vascular effects of, *29* (Abst.)
Phenobarbital, exfoliative dermatitis and hepatitis due to, *84* (Abst.)
Phenolphthalein, contact dermatitis due to, *7* (Abst.)
Phenylmercuric acetate, efficiency of, as a preservative in antigens (Williams and Piness), 45
Physiotherapy in asthma, *19* (Abst.)
Piperazine compound, a new, clinical application of, *44* (Abst.)
Pitressin, hypersensitivity to, *23* (Abst.)
Pituitary adrenocorticotrophic hormone, administration of, effect of, on Loeffler's syndrome and tropical eosinophilia (Herbert et al.), 12
effect of, on histamine intoxication and anaphylaxis in guinea pig (Friedlaender and Friedlaender), 303
therapy, effects of, *74* (Abst.)
Plant disease, spore dispersal in relation to, *18* (Abst.)
Pneumonitis, experimental production of (Jahiel and Jahiel), 102
Pneumothorax, recurrent spontaneous, asthma complicated by (Wiseman et al.), 199
Poison ivy treated with aqueous (alum precipitated pyridine) extract, summary of 100 cases (Gaillard), 55
Pollen, atmospheric, preliminary report on study of, *66* (Abst.)
ragweed, determination of specific gravity of, and conversion of gravity sample counts to volumetric incidence, *66* (Abst.)

Pollen—Cont'd
Survey Committee of the American Academy of Allergy, report of, for season of 1949 (Durham), 442
tolerance nasal tests in hay fever, experimental and clinical observations (Tuft and Blumstein), 326
Pollen-counting guide (Credille), 78
Pollens, allergic specificity of, *34* (Abst.)
ragweed and oak, air-borne, at Columbus, Ohio, volumetric and gravity slide tests for, *49* (Abst.)
Polyarteritis nodosa, acute, in childhood, *9*, *44* (Absts.)
of coronary arteries, *44* (Abst.)
Postnasal mucoid material, rubber-tip suction as aid to obtaining (Price), 179
Potassium and acetylcholine, sensibility of skeletal muscle to, effect of antihistaminic drugs on, *61* (Abst.)
Precipitin production in chickens, *64* (Abst.)
Pregnancy, histamine administration during, *12* (Abst.)
metabolism in, *11*, *62* (Absts.)
Pregnant women, effect of treatment with an antihistaminic drug on blood pressure and urine in, *93* (Abst.)
Procaine, contact dermatitis due to, *6* (Abst.)
"hypersensitivity," treatment with neostigmine, *88* (Abst.)
intravenous, anaphylactic reaction to, *55* (Abst.)
as analgesic agent, pharmacologic actions of, *12* (Abst.)
in children, *25* (Abst.)
Prophenpyridamine, toxic psychosis due to, *78*, *94* (Absts.)
Pruritus from chicken pox, treatment of, with Pyribenzamine, *80* (Abst.)
Psoriasis, a bacterial allergy, *86* (Abst.)
Psychosomatic medicine, principles and applications (book review), 565
phenomena in rhinitis and asthma, an experimental approach to (Wolf et al.), 1
Pulmonary edema, acute, failure of Phenergan to protect against, *90* (Abst.)
experimental studies of, *2* (Abst.)
embolism following injection of penicillin in oil and wax, *48* (Abst.)
resection, curative treatment of bronchiectasis by, *3* (Abst.)
Pyribenzamine, administration of, effect of various modes of, on histamine wheal and epidermal sensitivity reactions, *67* (Abst.)
adsorption, distribution and excretion of, *58* (Abst.)
agranulocytosis after prolonged use of, *78* (Abst.)
following, *32* (Abst.)
Pyribenzamine—Cont'd
and epinephrine, antihistaminic action of, introduced into human skin by electrophoresis, comparison of, *13* (Abst.)
dermatitis following use of (Sherman and Cooke), 63
effect of, on release of histamine during in vitro hemolytic reaction in rabbit blood (Carryer and Code), 314
on respiration of mouse brain homogenates, *92* (Abst.)
failure of, to protect against systemic tuberculin shock, *57* (Abst.)
iontophoresis of, in allergic rhinitis, *69* (Abst.)
Neohetramine, and rutin, effect of, on reversed anaphylaxis in guinea pigs (Arbesman et al.), 25
therapy, acute urticaria following, *22* (Abst.)
treatment of pruritus from chicken pox with, *80* (Abst.)
unusual reaction following use of, *32* (Abst.)
Pyridine, alum precipitated, poison ivy treated with, summary of 100 cases (Gaillard), 55

Q

Quinidine allergy, *92* (Abst.)

R

Ragweed and oak pollens, air-borne, at Columbus, Ohio, volumetric and gravity slide tests for, *49* (Abst.)
antigen, effect of slowly absorbing, on neutralizing antibody titer (Malkiel and Feinberg), 525
dermatitis, therapy by oral route, *6* (Abst.)
pollen, determination of specific gravity of, and conversion of gravity sample counts to volumetric incidence, *66* (Abst.)
effect of cortisone on hay fever and asthma in subjects sensitive to (Carryer et al.), 282
Reagin formation, factors influencing, in experimental human sensitization to *Ascaris lumbricoides* antigen. IV. The influence of previous sensitization on rate of sensitization (Kailin et al.), 225
Respiratory allergy due to fungi, *65* (Abst.)
in children, treatment of, by oral administration of dust and pollen extracts (Black and Holman), 148
diseases, allergic, mold fungi in etiology of, *49*, *50* (Absts.)
exercises in asthma, *19* (Abst.)

Respiratory—Cont'd
tract, infections of, gamma globulin in relation to, *23* (Abst.)
Rh factor, misconception concerning, and the interruption of pregnancy, *79* (Abst.)
Rheumatic disease, diagnosis of, failure of sensitized sheep cell agglutination to clarify, *14* (Abst.)
fever, pathogenesis of role of allergy in, *27* (Abst.)
serological studies in, *8*, *79* (Absts.)
Rheumatoid arthritis, serological reactions in, *63* (Abst.)
Rhinitis, allergic and vasomotor, treatment of, with hesperidin chalcone sodium, *39* (Abst.)
psychosomatic phenomena in experimental approach to (Wolf et al.), 1
Rhus toxicodendron dermatitis, prophylaxis of, *83* (Abst.)
Rubber-tip suction as aid to obtaining postnasal mucoid material (Price), 179
Rutin, Pyribenzamine, and Neohetramine, effect of, on reversed anaphylaxis in guinea pigs (Arbesman et al.), 25

S

Saprophytic fungi, air-borne, collection and identification of, tests of different media for (Swaebly et al.), 404
Schoenlein purpura associated with hematuria, *41* (Abst.)
Sensitivity, castor bean (Figley and Rawling), 545
corn, clinical experience in (Figley and Rawling), 510
diagnostic tests in, clinical experience with objective (Cazort), 512
egg white, skin test reactions to chemical fractions of, clinical significance (Miller and Campbell), 522
reactions to aureomycin, *68* (Abst.)
skin, to penicillins G, BT, and O; demonstration of cross-sensitization (Risman and Boger), 425
to streptomycin (Simon), 400
tissue, changes in, associated with varying life situations and emotions; their relevance to allergy (Graham et al.), 478
to ammoniated mercury; treatment with BAL, *68* (Abst.)
to aureomycin, *83* (Abst.)
to cane sugar, *86* (Abst.)
to cinnamon, *84* (Abst.)
to foods, specific, as factor in eczematous dermatitis, *22* (Abst.)
to Furacin, *67* (Abst.)
to mercurial diuretics, *20* (Abst.)
to phenobarbital, *84* (Abst.)
to sesame seed and sesame oil, *41* (Abst.)
to vitamin B_{12} concentrate, *69* (Abst.)
Sensitization, eczematous, to a drug, effect of development of, on the pharmacologic properties of that drug (Rostenberg et al.), 217
experimental eczematous, failure to prevent (White and Baer), 344
mucous membrane, studies in, *38* (Abst.)
to Antistine, *53* (Abst.)
to *Ascaris lumbricoides* antigen, experimental human, factors influencing reagin formation in. IV. The influence of a previous sensitization on rate of sensitization (Kailin et al.), 225
to para-aminosalicylic acid, *41* (Abst.)
Serum fibrinolysin, release of, by specific antigen, peptone, and certain polysaccharides, observations on, *73* (Abst.)
hypersensitive (allergic), in vitro release of histamine by, in contrast to immune (treated) allergic serum in antigen and normal rabbit blood mixtures (Spain et al.), 318
hypersensitiveness, experimental, inhibitory effect of nitrogen mustard on lesions of, *45* (Abst.)
proteins in diseases of connective tissue, *52* (Abst.)
sickness in rabbits, experimental, plasma volume and extravascular thiocyanate space in, *43* (Abst.)
Sesame seed and sesame oil, sensitivity to, *41* (Abst.)
Shock, acute allergic, blood examination in hay fever patients during, *51* (Abst.)
anaphylactic, role of adrenal glands in, in guinea pig, *87* (Abst.)
burn, effect of tripelennamine hydrochloride in, *47* (Abst.)
experimental, antihistamine therapy in, *92* (Abst.)
tuberculin, failure of Pyribenzamine to protect against systemic, *57* (Abst.)
Shwartzman phenomenon, inhibition of, by ACTH from the adenohypophysis, *61* (Abst.)
with penicillin, *9* (Abst.)
Sinus disease with asthma; comparison of radical sinus surgery and conservative treatment (Guerrant et al.), 187
Sinusitis due to bacterial allergy, *54* (Abst.)
Skin protection in radiation therapy, antihistamine ointments for, *21* (Abst.)
reactions, *13* (Abst.)
sensitivity to penicillins G, BT, and O; demonstration of cross-sensitization (Risman and Boger), 425
to streptomycin (Simon), 400
test reactions, chemical fractions of egg white, clinical significance (Miller and Campbell), 522

Skin—Cont'd
xylene-treated, effect of antihistamine on localization of trypan blue in, *12* (Abst.)
Sludged blood in allergy, role of, *61* (Abst.)
Smallpox vaccination, reaction to, immediate, *86* (Abst.)
Sodium salicylate, effect of, upon hypersensitivity reactions, *87* (Abst.)
Splenectomy, effect of, on formation of circulating antibody in adult male albino rat, *88* (Abst.)
"Spontaneous" flare-up phenomenon, observations on (White and Baer), 344
Spore dispersal in relation to plant disease and health, *18* (Abst.)
Spores of *Hormodendrum resinae*, intramural dissemination of (Christensen), 409
Status asthmaticus, *33* (Abst.)
acute parietal endocarditis in case of, *82* (Abst.)
Sting of bee, histology of lesions caused by, *70* (Abst.)
Streptomycin, exfoliative dermatitis due to, *52* (Abst.)
skin sensitivity to (Simon), 400
therapy, cutaneous lesions occurring in course of, *36* (Abst.)
Sugar alcohols; drug allergy in canine family, *25* (Abst.)
cane, allergic reactions from ingestion or intravenous injection of, *86* (Abst.)
Sulfobromophthalein sodium, anaphylactoid reaction to, *70* (Abst.)
Sulfonamide "fixed eruption," *36* (Abst.)
Suprarenal cortex in allergic diseases, investigations of functions of, *59* (Abst.)
Sympathomimetic amines, action of, on central nervous system and the blood sugar, *89* (Abst.)
Symposium on food allergy, American Academy of Allergy, sixth annual meeting, Los Angeles, Calif., March 6-8, 1950, 471

T

Tetanus antitoxin, myocardial infarction following administration of, *29* (Abst.)
Tetraethylthiuram disulfide, fixed drug eruption from, *68* (Abst.)
Theophylline ethylenediamine, administration of, *77* (Abst.)
Thephorin Ointment, clinical and experimental evaluation of (Reiss and Kern), 160
reactions to local use of, *5* (Abst.)
therapy, studies on topical: index of sensitization and effectiveness as an antipruritic (Stritzler), 432
Thrombophlebitis migrans, antihistamine therapy in, *16* (Abst.)
Thrombotic thrombopenic purpura caused by iodine, *48* (Abst.)
Tissue sensitivity, changes in, associated with varying life situations and emotions; their relevance to allergy (Graham et al.), 478
Tobacco antigen, cutaneous reactions to, in allergic and nonallergic children, *55* (Abst.)
mosaic virus, immunochemical studies on, *80* (Abst.)
Tooth powder containing penicillin, effect of, on mucous membrane, *38* (Abst.)
Topical Thephorin therapy, studies on: index of sensitization and effectiveness as an antipruritic (Stritzler), 432
Trichinella spiralis, eosinophil response of rats infected with, effect of adrenalectomy on, *12* (Abst.)
Trichophytin, edematous reactions to, immediate wheal and 24-48 hour tuberculin type, *5* (Abst.)
Tridione and Paradione in treatment of epilepsy, comparison of, *67* (Abst.)
Trimeton, toxic psychosis due to, *78*, *94* (Absts.)
Tripelennamine, action of, on hyaluronidase in albino rat, *28* (Abst.)
adsorption, distribution and excretion of, *58* (Abst.)
hydrochloride, agranulocytosis after prolonged use of, *78* (Abst.)
effect of, on acute inflammation, *77* (Abst.)
on burn shock, *47* (Abst.)
on release of histamine during in vitro hemolytic reaction in rabbit blood (Carryer and Code), 314
Tropical eosinophilia, effect of administration of ACTH in (Herbert et al.), 12
Tuberculin and histoplasmin, doubtful reactions to, *80* (Abst.)
cutaneous hypersensitivity to, in man, cellular transfer of, *54* (Abst.)
cytolysis, in vitro, leucocyte blockade of, *30* (Abst.)
isolation of proteins and polysaccharides from, by alcohol fractionation, *80* (Abst.)
patch test, pseudoreactions to, *15* (Abst.)
type reaction by antihistaminic drugs and rutin, inhibition of, *41* (Abst.)
shock, failure of Pyribenzamine to protect against systemic, *57* (Abst.)
Tuberculoprotein, in vitro lysis of leucocytes by, a plasma factor responsible for, *30* (Abst.)
nature of plasma factor responsible for, *40* (Abst.)
lysis of leucocytes by, role of complement in, *40* (Abst.)

U

Undecylenic acid, dermatitis medicamentosa due to, *53* (Abst.)

Urticaria, acute, following Pyribenzamine therapy, *22* (Abst.)
and angio-edema in association with amebiasis, *83* (Abst.)
chronic, due to *Giardia lamblia*, *20* (Abst.)
cold, passive transfer of (Sherman and Seebohm), 414
due to Mercupurin, *20* (Abst.)
photogenica, *21* (Abst.)
Uveal infiltration, histamine and, *23* (Abst.)

V

Vaccine, chick embryo propagated, immunologic response of children to injection of, *95* (Abst.)
Vascular diseases due to hypersensitivity, *45* (Abst.)
Ventilatory tests in bronchial asthma (Gaensler), 232
Virus vaccine immunization against the common cold, *31* (Abst.)
Visammin (khellin), clinical use of, observations on, *51* (Abst.)
Vital capacity and maximum breathing capacity, evaluation of (Gaensler), 232
Vitamin B_{12} and parenteral liver therapy, allergic reactions to, *70* (Abst.)
concentrate, sensitivity to, *69* (Abst.)

W

"Wax" of tubercle bacillus, role of, in establishing delayed hypersensitivity, *72* (Abst.)
Whealing phenomena, effect of antihistamine agent on various, *11* (Abst.)
reaction, effect of various drugs on, study of (Mosko and Marshall), 242
Wood, bronchial asthma caused by, *66* (Abst.)
dust as inhalant allergen, *66* (Abst.)
bronchial asthma caused by inhalation of, *18* (Abst.)

X

X-ray radiation, effect of, on hypersensitiveness (Criep et al.), 373